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CONTACT DERMATITIS

As a Problem in the Army from the Standpoint of Diagnosis and Treatment, with the Presentation of Photographs and a Discussion of Several Interesting Case Records

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"SKIN diseases are of greater importance in the military service than in civil life." This statement was made by Major General James C. Magee when he was Surgeon General. Although there are few deaths from skin diseases, they do result in a considerable loss of effective manpower and a partial incapacity of a number of personnel of many commands.

The latest available figures (1940) of the U. S. Army[2] indicate that skin diseases, exclusive of syphilology, produced 9.80 per cent of all admissions to the sick list and 10.41 per cent of all days lost. The figures for the United States Navy are very nearly the same. It is to be noted also that these figures are all peacetime statistics and that the diseases in these groups have always experienced a rapid relative increase during periods of military mobilization and actual combat. It is well known that the increase of skin disease is relatively greater than the increase of disease in other organs or systems. The major number of soldiers who report on sick call with skin disease remain ambulatory. The figures mentioned above, therefore, would indicate fewer than half their actual occurrence.

The skin is continuously exposed to a great number of ordinarily harmless substances, few of which are primary irritants, but which may induce contact dermatitis.[27,33] It is to be understood that the reaction of primary irritants on the skin is one of trauma and may be produced by

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acids or alkalies. The resulting injury is not to be confused with the fact that anyone can be sensitized to contact with a dye or chemical, vegetable or weed, if the exposure is sufficiently prolonged and sufficiently intense. This resulting sensitization of the skin is often accelerated by a previous exposure to a primary irritant, as, for example, in the cook who washes his hands frequently with GI soap and becomes sensitive to the vegetables which he prepares.

The occurrence of contact dermatitis is probably greater than the incidence of all other allergic skin diseases, and as a group they constitute the most commonly encountered of all skin diseases.[1,3,19,35] Among the civilian population, the problem of contact dermatitis[9] had reached such proportion, particularly at the time when every man was needed, as to be considered a form of industrial sabotage. Louis Schwartz[26] of the United States Public Health Service has stated that more time is lost from work on account of occupational dermatitis than because of any other occupational disease. The increase in the number of these cases is due mainly to the increased industrial expansion which has taken place, the drive to attain peak production, and the secondary consideration given frequently to the matter of health hazards. The importance which this rising cost in manpower has reached has shown the need for immediate specific action. The Council of Industrial Health of the American Medical Association, realizing the great importance of this situation as it would affect our war effort were it allowed to continue, has sponsored an all-inclusive Industrial Health program.[10] The transfer into the armed forces of a considerable proportion of our working population, with the introduction of new environmental contacts, has made the problem of contact dermatitis in the Army one of great importance from the standpoint of diagnosis, treatment and final disposition.

The result of treatment in any disease depends upon correct diagnosis; this is especially true in contact dermatitis. The clinical and environmental history, symptoms, distribution of skin lesions, special tests and differential diagnosis will clearly point to the condition in question and enable one to treat properly a given problem and to evaluate correctly its cause and implications.

A few years ago, conditions of contact dermatitis were designated dermatitis venenata or occupational dermatoses, depending upon the nature of the excitants or the circumstances under which contact occurred. If, for example, the excitant was a constituent of a plant of the Rhus, such as the so-called poison ivy, poison oak or poison sumac, the condition was spoken of as dermatitis venenata, and the exciting substances in these plants were considered to be poisons. If, on the other hand, the dermatitis occurred among factory workers who handled certain chemicals such as T.N.T., iodoform or the dye paraphenylenediamine, the term occupational dermatoses was often used. Cran-

ston Lowe[17] in his book on Anaphylaxis and Sensitization, recognizing the identity of these conditions with those produced by the non-protein excitants of plants, describes them as "dermatitis venenata due to chemicals other than those contained in plants." However, when it was found that animals and also almost all city-born children under five years of age are completely insusceptible to the first contact with the strongest extracts of poison ivy, it became evident that the dermatitis caused by this plant was not due to any primarily toxic principle in it.[32] This observation left no further doubt that dermatitis venenata is a special instance of a specific cutaneous sensitivity which is acquired by and is exhibited upon surface contact with the excitants found in poison ivy.

The allergic nature of dermatitis venenata was demonstrated by the experiments of Brown, Milford and Coca,[6] Cranston Lowe[17] and especially Bloch[4] with primrose. These investigators could show that, whereas most persons are insusceptible to the juice or extract of primrose and other plants, many persons acquire a sensitivity to the plant after one or more exposures by surface contact. Bloch, using a concentrated extract of primrose, could sensitize all of the twelve subjects of his experiments.

CHARACTERISTICS OF CONTACT DERMATITIS

Contact dermatitis differs characteristically from the inherited group of allergic diseases (bronchial asthma, hay fever, infantile or atopic eczema, urticaria, migraine)[12] and its ultimate diagnosis and proper treatment by the medical officer often depend wholly upon his recognition of these differences. A very significant difference between contact dermatitis and atopic eczema is the fact that an atopic hereditary influence seems to control the development of atopic eczema, but plays no part in the etiology of contact dermatitis. Individuals who develop atopic eczema usually have an atopic influence in their antecedent family history and often have hay fever or asthma at the time or later in life. However, contact dermatitis occurs where there is no atopic basis and may appear among the majority of those who are exposed for a long period of time to a particular excitant. Furthermore, in atopic eczema, usually no reaction occurs when the excitant is applied to the skin, but in contact dermatitis, the application of the exciting substance to any area of the skin usually causes a lesion of the same type. If the excitant is injected intradermally in an area which is free of lesions, wheal formations will usually occur in atopic eczema and skin-reacting antibodies are most often found in the blood. In the case of contact dermatitis, this wheal formation does not take place, and the skin-reacting antibodies are not present.[7]

There is no difficulty in tracing the simple instance of a contact dermatitis from which a soldier always suffers following the use of a certain shoe dye or which appears after a specific, dyed, fur-lined jacket is worn.

In such a case, if the patient has not already noticed the casual connection and acted accordingly, the medical officer simply advises the banishment of the offending material. On the other hand, when the patient is a pharmacist whose torturing eruption disappears if he avoids his daily contact with drugs, or when the attacks are seasonal and coincide with the pollination period of a hay-fever-causing plant, the problem is more complex. In either of these situations, if the medical officer is aware of the allergic nature of the dermatitis, not only must he resort to cutaneous tests in order to identify the exciting cause (plant or pollen) but he must choose the proper kind of test material and also the proper method of applying the cutaneous test.

An understanding of the symptoms and distribution of contact dermatitis will enable one to further clinch the diagnosis. Given a case of contact dermatitis, the history elicited will be one of sudden onset and the skin most severely involved will be that part of the body most exposed to the contactant. At first there will be an area of erythema limited to the area of contact, which is soon followed by edema, vesicle formation and subsequently weeping and crust formation. In cases which are not acute, the initial lesions need not be vesicles, but may be papular in character, with moderate edema and erythema. In several days this condition will result in a mild erythema and desquamation. If the process is one of a chronic nature, the area involved will present a bluish-gray discoloration. Later, thickening, lichenification, and desquamation will take place.

Marked itching is generally present in all stages of contact dermatitis, although during the height of the eruption, the pruritis may diminish noticeably. Secondary infection often complicates the picture, producing pustules, scabs and associated stinging, burning and pain.

Although no area of the skin is immune to contact dermatitis, certain areas of the skin surface are more easily affected. The exposed skin of the face, neck, especially the "V" area, the anterior part of the chest, upper extremities, legs and ankles are usually the sites of predilection. Specific contact allergens may be suspected when a dermatitis of the type described appears in a particular area of the body. It is, therefore, very important to establish the site of the first appearance of the dermatitis and its subsequent spread. The important areas[34] of involvement with possible contact allergens are shown in the accompanying table.

TESTS

The well-known skin tests[25] for determining the excitants of asthma, hay fever, infantile eczema, gastro-intestinal allergy and allergic headache are carried out by the intracutaneous injection of aqueous extracts of various materials or by rubbing the extracts into an abrasion in the skin produced with a needle or scalpel (scratch method). The exciting substances in these aqueous extracts are usually of protein nature and

CHARACTERISTIC SITES OF ECZEMATOUS CONTACT DERMATITIS AND THEIR COMMON CAUSES*

Localization	*Suggested Causes*
1. Scalp† and forehead	1. Scalp lotions; scalp tonics, pomades, etc., caps and hats and their bands, linings and other materials.
2. Eyelids (one of the most sensitive areas)	2. Numerous substances used on scalp, face, and hands, soaps, shaving lotions, creams, powders. Airborne volatile agents and dusts (plant pollens, insect sprays, gaseous substances; nasal sprays, cleaning fluids, antimoth preparations, perfumes, benzene; dusts from clothing, furniture; materials of dyed clothing, fabrics, furs, gloves, etc.).
3. Face in general	3. All possible materials transferred by hands or air-borne. All substances used on face, scalp, or hands. Shaving soaps, after-shaving lotions, etc., gas masks, etc.
4. Ears and retro-auricular areas	4. Scalp lotions, salves, spectacles, goggles, ear muffs, etc.
5. Nose and nasolabial areas	5. Nose drops, nasal ointments, sprays, etc., handkerchiefs, paper tissues, etc.
6. Lips and perioral areas	6. Mouthwashes, tooth pastes, powders. Sometimes certain foods (oranges, other citrus fruits and their juices).
7. Neck: front, sides and/or back	7. Collars, scarves, neckties, clothing, fabrics (wool and dyes) substances used on scalp.
8. Sides of neck, upper chest, wrists, cubital spaces, inner and anterior aspects of thighs, ankles, and lower legs and dorsa of feet	8. Typical of clothing materials and their dyes; "uniform" or "wool" dermatitis.
9. Hands, forearms, and face	9. Substances too numerous to list. Most occupational and industrial excitants. Substances encountered in military activities, plants (ivy, etc.); gasoline, greases, paints, chemicals, soaps, cleansers, gloves, steering wheels, instruments or substances encountered in hobbies or games; or topical medicaments applied to self or to others; all objects which may be touched, handled, held, or worn.
10. Trunk, various sites	10. Clothing, plants, underwear, night clothes, sweaters, bathing materials, soaps.
11. Perianal	11. Feces and decomposition products (cleanliness! thorough washing after defecation, no toilet paper), substances in enemas, suppositories, intestinal parasites, ingested foods (fruits, oils), topical medicaments, underdrawers, toilet paper, etc.

(See following page)

*Based mainly on a table in Sulzberger, M. B., and Wolf, J.: Dermatologic Therapy in General Practice. Chicago; The Year Book Publishers, 1940.

†The scalp is often remarkably resistant to external irritants and allergens. Thus, dermatitis caused by substances used on the scalp often appears not primarily on scalp but predominantly or exclusively on other, more sensitive skin areas, such as eyelids, ears and retro-auricular areas, nape and other parts of neck, face in general, and even the hands.

CHARACTERISTIC SITES OF ECZEMATOUS CONTACT DERMATITIS AND THEIR COMMON CAUSES

(Continued)

Localization	*Suggested Causes*
12. Penis and scrotum	12. Substances carried by the hands: plants, clothing, medicaments used for pediculosis, chemical prophylaxis, fungous infections, etc.; fabrics, finishes and dyes in underdrawers, pajamas, rubber and elastic supporters.
13. Thighs, legs, and ankles	13. Dyed materials and materials of trousers, underdrawers, socks, etc.; match boxes, cigarette lighters, coins, and other metallic objects carried in trousers, pockets, etc.; volatile and air-borne substances, dust (inside trousers), etc.; plants.
14. Lower portions of legs and feet	14. Shoes, socks, stockings (leather dyes, tanning agents, dyes, and finishes of materials, etc.); plants.
15. Feet (particularly dorsa of great toes), sides and dorsa of feet and sometimes soles (often with little or no interdigital involvement)	15. Shoes, leather dyes, tanning agents, shoe polishes, sock dyes and finishes, rubbers, etc.
16. More or less generalized eruptions	16. Any of the aforementioned agents may produce not only localized but generalized eczematous dermatitis. Also, medicaments taken by mouth or injected (arsenicals, quinine, salicylates, hexamethylenetetramine, etc.)
17. Contacts in the Army and location of the dermatitis	17.
(a) Face	(a) Gas masks.
(b) Chest and wrists	(b) Identification (dog) tags and metal buttons from uniforms and fatigue clothes.
(c) Arms	(c) Chevrons.
(d) Legs	(d) Paratrooper boots, GI shoes and socks.
(e) Generalized	(e) O.D. clothes (clothing dermatitis), oriental dye dermatitis[18], penicillin contact dermatitis.

they are all antigens (capable of stimulating antibody production in animals).

In contact dermatitis due to vegetable or other excitants, on the other hand, the intracutaneous and scratch methods usually give negative results, especially with aqueous extracts, even when these extracts are prepared from the known excitant of the dermatitis. For this condition, it is necessary to use the surface contact or patch test which was first employed by the European dermatologist, J. Jadassohn.[13,14,15] This simple test merely reproduces the conditions of natural contact, and the resulting positive reaction represents nothing but the typical lesion of contact dermatitis.

The patch test may be carried out with the crude suspected material

(powder, leaf, fur, foodstuffs, chemicals) by placing it upon the skin (usually of the arm) and maintaining contact with wax paper or cellophane on a strip of adhesive plaster, or, as suggested by M. Walzer[37], with a circle of cellophane rimmed with collodion or with the celluloid device of Aaron Brown.[5]

Aqueous extracts of vegetable excitants of contact dermatitis usually contain so little of the excitant that they do not cause reactions in the patch test. The reason is that these vegetable excitants are of fatty nature, and, therefore, only slightly soluble in water. However, they are easily extractable with fat solvent by evaporation, the fatty or oily residue is readily soluble in oils such as olive or almond oil. This oily fraction may be utilized for the purpose of eliciting patch test reactions.

The contact test is one of our most valuable clinical procedures, because it is a direct test of the clinically susceptible tissue, the epidermis; the positive reaction really reproduces the clinical lesions. The test seldom fails, if active and sufficiently concentrated material is used. Various techniques are available, depending upon the material being tested; the ideal procedure is the following:

(1) An undiluted oily or resinous extract should be applied to a small area of untraumatized skin (rubbing is usually unnecessary); the area is covered, for protection and for limitation of reaction, as noted above, with a square of white blotting paper about one-quarter inch in diameter set in the center of a large square of cellophane or wax paper and then a still larger square of adhesive plaster.

(2) A similar technique can be employed if the test material consists of dry powder. The dry powder is applied directly to the skin.

(3) Raw materials may also be used, such as a leaf which has been crushed before being placed on the skin, a piece of fur, suspected pollen, or dust. Such tests are, of course, less expensive and more readily available than those with the extracted oils and they are probably just as reliable. However, after a positive response with the raw materials, if specific treatment is contemplated, it is advisable to do the patch test again, using the extracted oil or an alcoholic extract.

Contact is maintained for twenty-four to forty-eight hours. The site should be kept under daily observation for five days before the reaction can be safely considered negative. When the reaction begins early, the patient should be instructed to take off the patch or report to the medical officer as soon as distinct itching is noticed. The oil should be removed thoroughly with alcohol or ether. This precaution is advised to prevent any unnecessary dermatitis.

Like other forms of allergy, contact dermatitis may be due to more than one excitant, and the patient may be found sensitive by contact test to an excitant which is not producing the clinical dermatitis under

investigation at the time. For example, a painter may suffer severe dermatitis and a contact test may show that he is highly sensitive to poison ivy; yet, his dermatitis may not be due to poison ivy, but to the turpentine in his paints. In other words, it is important, before treatment is begun, that the result of the patch test be corroborated by the clinical history.

A positive reaction indicates hypersensitivity of the skin to the particular substance tested, but does not necessarily indicate that this substance is the cause of the existing dermatitis. The test must reproduce some phase of the existing dermatitis, such as erythema, edema, vesiculation and intense itching. It must further be indicated in a history of exposure to this substance.

In a negative reaction one must be certain that the substance tested is the one suspected according to the history, and that it is in the proper concentration. Also the area tested may have undergone spontaneous desensitization. It may be necessary to test a former area of dermatitis, since it may have become hypersensitive. The "V" of the neck is often productive of positive patch tests[36] when the arms are negative. This is especially true of facial contactants.

Polyvalent hypersensitivity in contact dermatitis is as common as it is in atopic eczema and makes for certain difficulties in deciding which substance is responsible; here the history will give the needed clue. Also, trial and error tests will assist in making the final decision.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is important, as there are a number of dermatoses which may be confused with contact dermatitis, as, for example, soldiers with a fungous infection[20] of the feet, together with a trichophytid[38] of the hands, a commonly made diagnosis, which is probably incorrect in at least half of the cases. A contact dermatitis of the feet. i.e., shoe dye dermatitis, may also produce vesiculation of the palms. Another vesicular eruption of the palms is cheiropompholyx, found chiefly in women, especially in those of a psychoneurotic background, particularly during the summer months. With atopic eczema, there is a personal or family history of clinical allergy. Nummular eczema, sharply marginated, coin-shaped plaques studded with punctuate vesicles, is found usually on the dorsal surfaces of the hands. Seborrheic eczema is associated with involvement of the palms and soles. Here the history and involvement of other areas are significant. There are also the skin diseases such as herpes simplex or herpes zoster which must be considered. The secondary skin lesions known as bacterids[23,31] which are the result of a toxic reaction from some focus of infection may resemble contact dermatitis, especially if the hands or feet are involved. An eczematoid dermatitis from primary irritants such as rubefacients, turpentine,

gasoline, benzene, acids, alkalies, may be differentiated by a careful history, as noted above. Infectious eczematoid dermatitis such as impetigo, ecthyma, and simple folliculitis must also be kept in mind. Yeast infections, associated with onychia, paronychia, perleche and intertrigo, presenting an erythematous, glazed skin with scaling, must not be overlooked. A long standing scabies, dermatitis herpetiformis, erythema multiforme, drug eruptions, lichen planus, psoriasis, syphilis, and others may be confused with a contact dermatitis if the examination is not of the most painstaking character.

TREATMENT

It should be born in mind that the treatment of contact dermatitis consists primarily of avoidance of the excitants to which the individual is allergic by contact and substitution or replacement if necessary and if possible of other substances to which he is not sensitive. However, it should also be remembered that having developed this highly sensitive skin, he may later become sensitized to the new materials. Where sensitization is to plants and avoidance is impossible, prophylactic measures and desensitization with oil extracts may be used.

Most plant extracts are available not only for the patch test but also for treatment, and it has been gratifying to discover that the results of specific treatment of contact dermatitis due to plants are as good as those obtained in the treatment of hay fever due to pollens. In this service command, the following method of treating poison ivy was employed and has been developed by Col. S. W. French, Surgeon to the Fourth Service Command, and Major Lawrence J. Halpin.[11] It is certainly the most convenient in the Army.

"A five per cent alcoholic extract of poison ivy leaves is prepared for active treatment. This is considered as a master extract and will deteriorate rapidly if diluted. In an undiluted form, its potency, as evidenced by a bright green color, will remain indefinitely. Institution of active treatment should be made and continued in the following manner:

"(a) Use a dry tuberculin 1 c.c. syringe and needle in order to prevent the addition of any water to this master extract.

"(b) Withdraw 0.1 c.c. of this master extract. Dilute it to ten times by the addition of 0.9 c.c. of normal saline or similar diluting fluid. Pull out the plunger a short distance to allow thorough mixing of the extract and the diluent.

"(c) In order to insure accurate dosage, all but the amount to be given in that one treatment is to be forced from the syringe prior to administration. The site of injection should be the lower third of the arm.

"(d) Improvement will usually be seen after the first or second treatment, and the dosage is increased gradually with each treatment, depending upon the amount of general reaction and the appearance of symptoms. The injections are given daily or every other day, according to the degree of reaction and the appearance of lesions.

"(e) The following is a brief schedule which may be used as an indication of the amount to be given at each treatment, using the above method of dilution:

First day: 0.1 c.c.	Fourth day: 0.3 c.c.
Second day: 0.2 c,c,	Fifth day: 0.35 c.c. (if necessary)
Third day: 0.25 c.c.	Sixth day: 0.4 c.c. (if necessary)

Great care must be taken in the administration of this extract to prevent an increase in the severity of lesions after an original improvement has been noticed. If there has been an exacerbation of the symptoms, it is best not to increase the dosage, but to decrease it or to repeat the same dosage. Mix each individual dose immediately before administration.

"(f) The above schedule need not be followed in each individual case, since it may be found that some individuals will respond to only two or three injections, whereas others may require four to five. Satisfactory results will usually be obtained by the proper use of this extract."

Other varieties of plant dermatitis may be treated successfully in the above manner. A single injection of 0.5 c.c. of 1 per cent solution of the oil of snap dragon in sterile almond oil has within twelve hours caused a complete disappearance of itching in a florist sensitive to this plant. In another instance, in civilian practice, (sensitivity in a florist to Gaillardia)[22] after three weekly injections of the oil solution had resulted in the disappearance of the dermatitis (although the patient continued to handle the plants), the treatment was discontinued in order to determine the longest interval of time at which the injections could be spaced without risk of a recurrence of the symptoms. After two months the skin lesions began to develop, indicating that about six weeks could be taken as the proper interval in that case.

Spain and Cooke[28,29,30] state that best prophylactic protection is obtained by beginning the injections early in April and continuing until frost. If alcoholic extracts are used, the first five doses (0.1 c.c. of 1-100, 1-50, 1-20, 1-10 and 1-5 dilutions of a 10 per cent alcoholic extract of the dry leaf) should be injected at weekly intervals. Thereafter, the fifth dose is repeated, at first at two or three weeks, then at monthly intervals.

If the ivy extract is administered in an oily base such as almond oil, the first dose can be about five times the maximal dose of the alcoholic extract and this dose can be repeated advantageously at two- or four-week intervals throughout the season. Evidently, the oily nature of the menstruum serves to reduce the rate of absorption of the injected extract and thus extends its effect over a longer period of time.

Spain and Cooke[28,29,30] also report that by quantitative patch test, no diminution in the skin sensitivity of a susceptible person could be detected after the successful application of specific prophylactic treatment by the injection method. Hence, as is also the case in hay fever, the degree of clinical tolerance to the excitant of contact dermatitis cannot be judged by the result of the quantitative skin test. However, they state that only four of the 98 patients so treated failed entirely to obtain relief from attacks of ivy dermatitis.

It is of some practical interest to medical officers in the United States to know the specific relationship of the three well-known excitants of plant dermatitis in this country, i.e., poison ivy, poison sumac, and poison oak. The close botanical relationship of these three plants would suggest a corresponding similarity of the active substances in them and this has

been verified by Henry W. Straus in some convincing experiments. Straus[32] sensitized newborn infants to poison ivy by skin surface application and then tested these sensitive children with extracts of the other two plants. The results of these tests were positive in all cases. These observations indicate that specific treatment of sensitivity to these three plants can be carried out with the extract of any one of them.

The specific treatment of contact dermatitis[2] due to animal contactants follows, in general, the therapy of Rhus dermatitis by injection of the extracted oily excitant. The allergenic oils are slightly soluble in water; in fact, the injection of saline pollen extracts has in a few instances caused the disappearance of a dermatitis due to the corresponding oil. However, in many patients a larger dose of the excitant oil is required for complete protection than can be provided in an aqueous medium. Furthermore, it is important that the oil be dissolved in a menstruum in which its specific activity will be preserved for a long period of time. Such a menstruum is sterile almond oil, which also possesses the valuable property of retarding the absorption of the dissolved excitant, thus extending its action over a longer period.

The routine of treatment differs in seasonal and non-seasonal cases:

1. If the dermatitis is seasonal, begin the injections about three weeks before the expected onset of symptoms. Give three doses at two-week intervals; a fourth dose may be given in mid-season and this should usually be sufficient. If lesions begin to appear later, further injections should be given.

If the treatment of a seasonal dermatitis begins during the season, (i.e., the lesions have already appeared), the first three injections, given at one to three-day intervals, may cause a rapid disappearance of the itching. Flare-ups may also occur, and it may be necessary to reduce the dosage. After the immunizing effect of the injected oil has been established, the healing of the existing lesions may require a period of weeks. This is in accord with the experience regarding the spontaneous healing of ivy poisoning after a single contact; these lesions sometimes persist for months after such contact. It must be understood that symptomatic treatment should be given during this healing period to assist in overcoming the irritation and in hastening recovery.

2. If the patient is continually exposed to the excitant, as in the case of a painter sensitive to turpentine, or a florist sensitive to a hothouse plant, the first three doses should be given at the shorter intervals (one to three days) and the injections should then be continued at five- to seven-day intervals until the lesions have disappeared. The frequency of the injections depends on the case, and no universal schedule can be given, because the degree of sensitivity and degree of tolerance varies with each individual and knowledge of what schedule should be followed must be based on experience.

3. It is to be understood that injections for metallic or other inorganic substances still await proper dosage and technique. At the present time, avoidance of these contacts is the method of choice. This is in accord with the experience of leading allergists and dermatologists.

Fig. 1. Case 1. Dermatitis of chest and wrists from metal contact (identification tags—"dogs", metal buttons on fatigue clothes).

The accompanying photographs are a representative cross section of the various cases of contact dermatitis which have been seen in our outpatient clinic and in our hospital service within the past year. Some of the more unusual ones are subsequently discussed.

DEMONSTRATIVE CASE RECORDS

Case 1.—The first case illustrated by photographs is that of a twenty-nine-year-old soldier who first developed a rash while he was out on maneuvers in 1941. The rash appeared first on his right wrist and it became generalized so that he had to be hospitalized at Camp Forest Station Hospital. His condition subsequently quieted down during his hospital stay, but he had to report from time to time to the outpatient clinic for repeated attacks of dermatitis on his chest and wrists, until he was again hospitalized on 27 June, 1943. Because his skin condition failed to respond to treatment, he was transferred to Oliver General Hospital 22 July, 1943 for further study, treatment and disposition.

Contact allergic history was significant in that the patient recalled always being sensitive to metals, especially during civilian life, when he was working as a mechanic in a garage. He also stated that he knew he was senstive to coins of any type.

Physical examination, aside from his dermatitis, was found to be essentially negative. The skin of the chest, abdomen and wrists was studded with reddish-blue

papules varying in size. The eruption was in various stages, revealing macules, papules, dried vesicles, many scratch marks and pigmented areas on the skin.

Laboratory examinations, including a complete blood study, serological tests and urinalysis, were negative. The scrapings from areas of the lesions revealed no fungi.

Fig. 2. Case 2. Dermatitis in a paratrooper from leather boots.

During the patient's stay in the hospital, he began to improve under mild soothing therapy, consisting principally of an aqueous lotion of zinc oxide, talc, bentonite, glycerin and water. When the skin showed sufficient improvement, he was then patch tested and found markedly sensitive to his metal "dog tags" and to the metal buttons of his fatigue uniform. He was also found very sensitive to mercury, copper and arsenic by patch testing. Various experiments, including the covering of his identification tags with chamois skin, cellophane, and x-ray film, were attempted in order to prevent recurrences of his dermatitis, but with little success, as the eruption would recur within twenty-four hours to seven days. Since there is no recognized treatment for metals other than avoidance, the failure of this technique made it necessary to discharge this man from the service because of his marked allergy to the various metals. A similar case was recently reported in *The Military Surgeon* of January, 1943, by Lt. Paul N. Unger, MC, U. S. Army.

Case 2.—A nineteen-year-old white soldier was admitted to Oliver General Hospital in July, 1943 complaining of a severe rash involving his feet and the lower two-thirds of his legs. This patient was a paratrooper and states that about one month after he started making his training jumps he developed some blisters

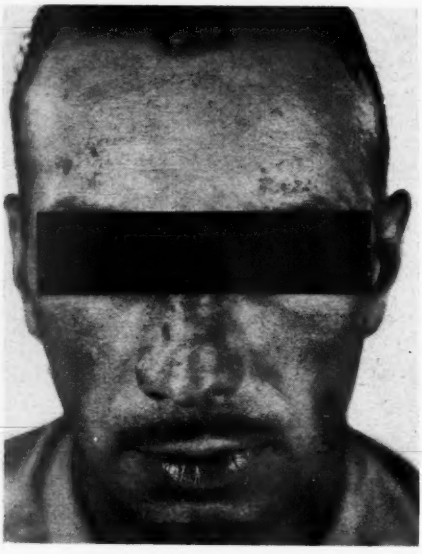

Fig. 3. Case. Dermatitis from contact with gas mask.

on his legs and feet. He reported on sick call for the blisters, which were very itchy. He states that his condition was diagnosed as athlete's foot and treatment was given for that condition. Because his dermatitis continued to become more severe, he was transferred to this general hospital for further treatment and disposition.

His contact and allergic history was essentially negative.

Physical examination, except for his dermatitis, was essentially negative. Over the skin of his feet there was a markedly pigmented, vesiculating, crusting dermatitis involving the dorsum of both feet and legs in the region of the ankles. There was no evidence of involvement on his soles or between his toes to suggest an epidermophytosis. In addition, there were macular, papular and vesicular lesions which covered the arms; crusts, probably due to secondary infection, covered most of the skin of the legs. The skin of the rest of the body was clear.

Laboratory examinations, including complete blood studies, serological tests and urinalysis were essentially negative. Smears from the skin lesions revealed no fungi.

It was our impression from the patient's history and physical findings that we were dealing with a contact dermatitis primarily due to the leather of his paratroop boots, which reached over halfway up his legs. This opinion was confirmed by patch tests. In these patch tests a piece of the tongue of his boots, as well as small pieces of material from his socks and other articles of clothing,

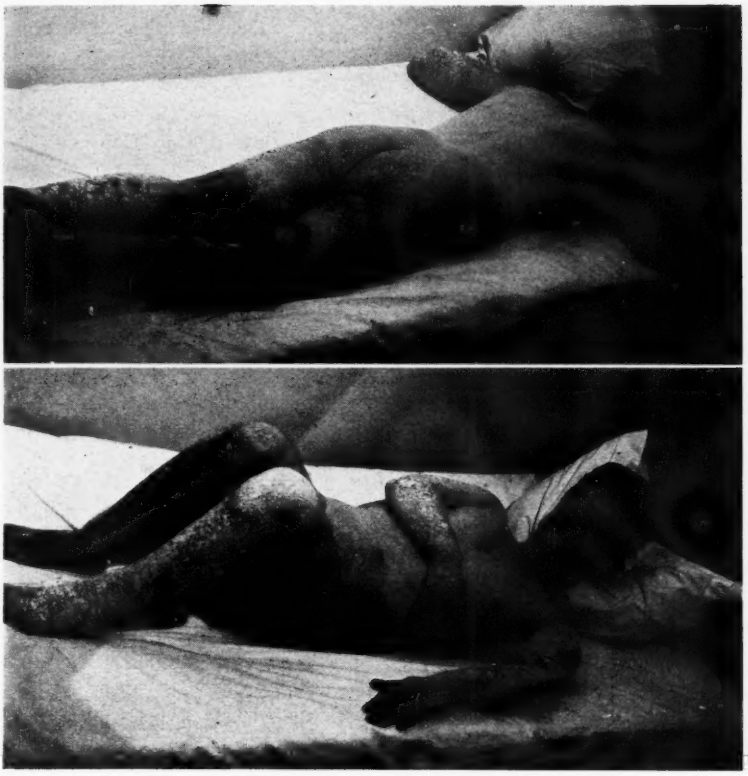

Fig. 4. Case 4. Dermatitis caused by repeated application of adhesive tape to feet and ankles with resulting, almost fatal, constitutional reaction.

was applied to the skin of his back. When these patches were removed for inspection, there was a marked reaction at the site of the leather contact. Under mild local medication, consisting of an aqueous solution of zinc oxide, talc, starch, bentonite and glycerin, his dermatitis rapidly improved, and since this patient was very eager to remain with his unit, a shoemaker was found who lined his boots with an impervious material, so that he was able to return to full duty. A recent letter from this soldier found him overseas and up to the present time he has had no recurrence of his dermatitis.

Case 3.—This photograph illustrates a type of dermatitis which is not infrequent in the Army. The patient in this photograph presented himself to the outpatient clinic of Oliver General Hospital with skin lesions on his forehead, on the lateral aspects of his face and on his chin. This dermatitis was thought to be due to contact with the rubber from the gas mask which he wore. This sensitivity to rubber was proven by a positive result to a patch test. A small segment of rubber from a gas mask was placed in contact with the patient's skin. After a period of forty-eight hours it was removed, revealing a marked reaction to the rubber. Other contactants, to which he was tested at the same time, gave negative results. An

effort was made in instances of this type to obtain a non-irritating rubber gas mask. A request regarding such a mask was made to the commanding officer of the Edgewood Arsenal and a reply was received from Brigadier General W. C. Kabrich, C.W.S., indicating that no such gas masks were available. Toxicity tests

Fig. 5. Case 5. Dermatitis caused by lubricating oil and grease, carried from hands to ears.

are made at the Edgewood Arsenal to eliminate primary irritants, but there are a number of individuals who will become sensitive to the materials of the gas masks. It was recommended by this officer that especially sensitive individuals be transferred to duty that would not require the wearing of a gas mask.[16] This advice was followed in the disposition of the soldier in this case.

Case 4.—A twenty-three-year-old soldier was admitted to Oliver General Hospital 2 October, 1943. On admission he appeared acutely ill with generalized exfoliative type of dermatitis associated with intensive itching, stinging and burning. The

patient stated that approximately six weeks previously he first noted an itching irritation about his ankles. This dermatitis appeared to be the result of several applications of adhesive tape to his feet and ankles. The adhesive tape had been applied because he had reported on sick call complaining of painful feet and

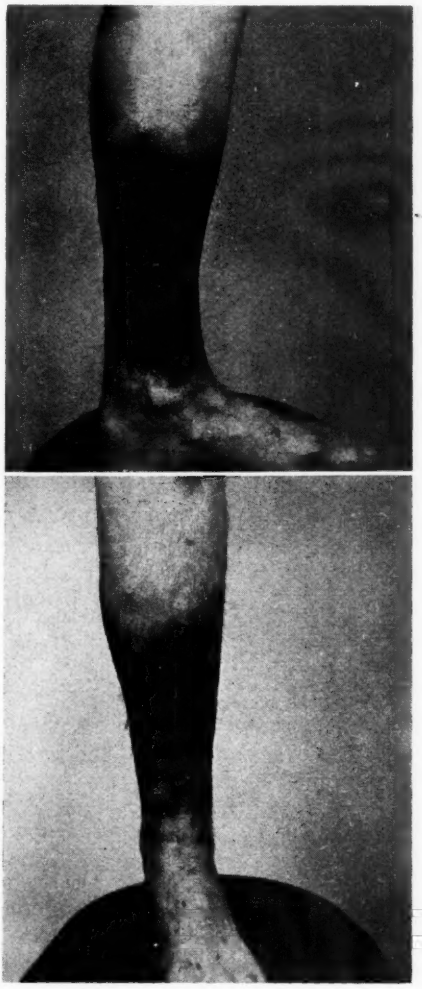

Fig. 6. Case 6. Dermatitis from sulfathiazole ointment and subsequent susceptibility to many greasy ointments, always with a return of symptoms.

ankles, especially after prolonged hiking. Although the pain in his feet and ankles had improved, and in spite of the irritation of his skin, the application and reapplication of adhesive tape to his feet was continued for about two weeks. The

eruption spread from the legs to the rest of the body, including the face, trunk and extremities, and he became very toxic.

His contact and allergic history was essentially negative.

Physical examination revealed an acutely ill white soldier who appeared toxic

Fig. 7. Case 7. Dermatitis due to pollen skin sensitivity to timothy and ragweed in a soldier who failed to respond previously to poison ivy extract.

with a generalized "oozing," vesiculating, desquamating dermatitis with marked itching. It was also associated with marked purpuric areas most noticeable over the lower extremities and lumbar region of his back. His lips were dry and crusted, but there were no apparent lesions in the mucous membrane of his mouth.

Laboratory examinations, including complete blood studies, revealed RBC 3,770,000, WBC 17,200, Hemoglobin 70, serological tests negative, normal blood

chemistry studies, and several granular casts and much mucus, but no blood, in the urine.

Because of the severity of this patient's dermatitis with marked toxic manifestations, he was placed on the critically ill list. He was given intravenous saline and

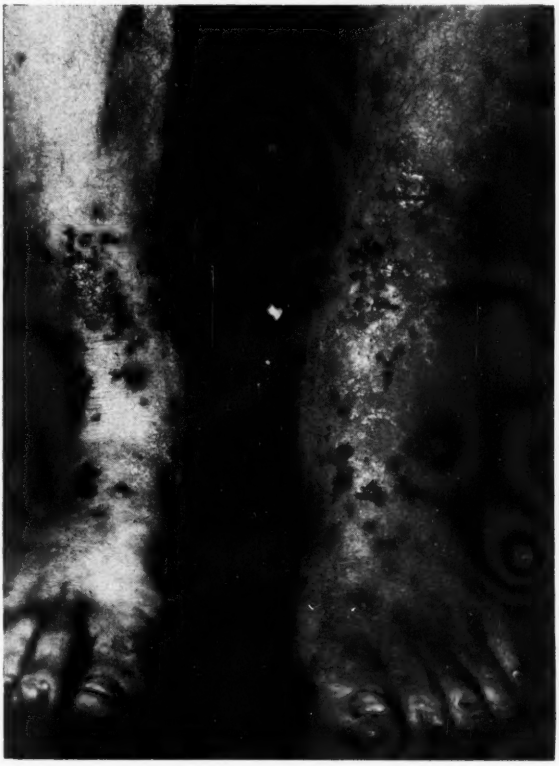

Fig. 8. Case 8. Dermatitis from dye in socks with superimposed secondary infection.

glucose and 200 mg. of cevitamic acid daily. Fluids of all types were encouraged, and a high caloric, soft diet was ordered. Medication by mouth was withheld, because of the possibility that drugs, especially of the sedative type, might accentuate this dermatitis. Local applications of boric acid and alum in the proportions of five parts of boric acid to three parts of alum in five hundred parts of water was used over his entire body, but this was apparently somewhat irritating. An aqueous lotion consisting of zinc oxide, talc, bentonite, tincture of ferric chloride and water was applied to his skin by means of a soft paint brush which had been previously sterilized. Within a period of seven days, the patient responded to the above outlined treatment, and he was removed from the critically ill list. His improvement continued satisfactorily and by Christmas of 1943 he was able to go home on sick leave. Upon his return, a mild dermatitis of his legs and ankles persisted in spite of all the various treatments which were used.

At this time his screen test to adhesive tape revealed an extremely marked hypersensitivity to the tape. It was, therefore, concluded that on the basis of his past personal history and his marked sensitivity to adhesive tape, that this was a case of a severe contact dermatitis due to adhesive tape. In January of 1944 he

Fig. 9. Case 9. Dermatitis due to Whitefield's ointment in a soldier with tricophytosis whose symptoms were accentuated with its application and who proved to be sensitive to salicylic acid.

was transferred to a Veterans Facility in order that his treatment might be completed.

Case 6.—This patient is a thirty-one-year-old soldier who was admitted to Oliver General Hospital in August, 1943, with a diagnosis of cellulitis. His history stated that this dermatitis followed an injury to his left leg, which occurred while he was out on maneuvers. He was admitted on the surgical service, and after examination was promptly transferred to the Allergy Department for study and treatment. It was found on studying the records that the injury was treated with sulfathiazole ointment and after this treatment he developed an itching eruption which spread rapidly, involving the lower half of his left leg. Treatment with various types of ointments failed to stop the spread of this dermatitis.

There were no associated constitutional symptoms.

His contact and allergic history was negative and there were no significant findings in his past history.

His physical examination was essentially negative except for the dermatitis.

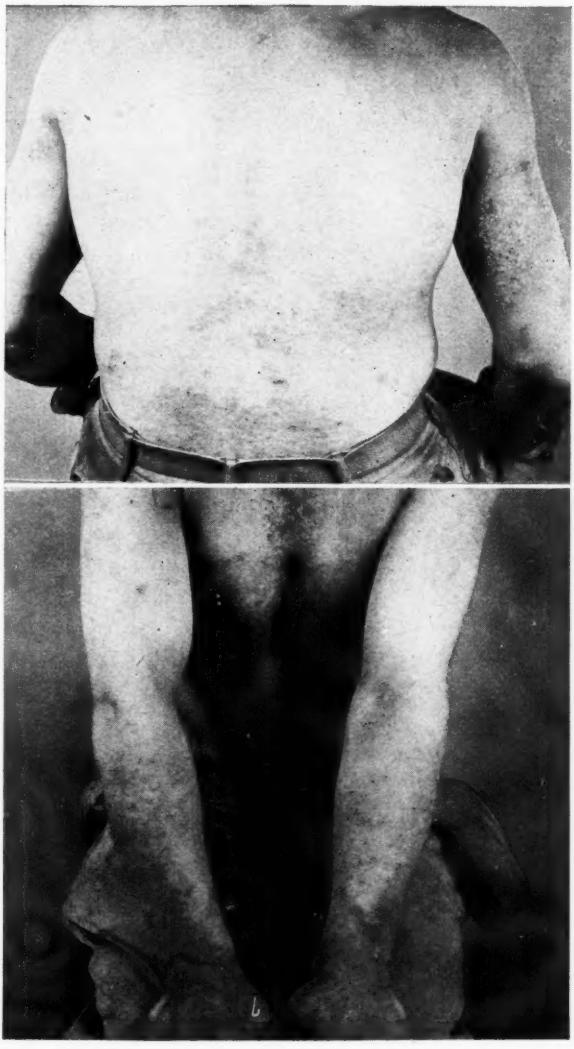

Fig. 10. Case 10. Dermatitis due to contact with wool and marked sensitivity to lanolin.

Fig. 11. Case 11. Dermatitis due to leather or dichromate from army shoes, beginning on feet and becoming generalized.

Over the skin of the lower half of his left leg there was a widespread eruption which appeared very acutely inflamed. Superimposed upon an erythematous base, there were numerous small pustules and vesicles which were very painful and itchy. Most of these lesions were covered by crusts, presumably the result of

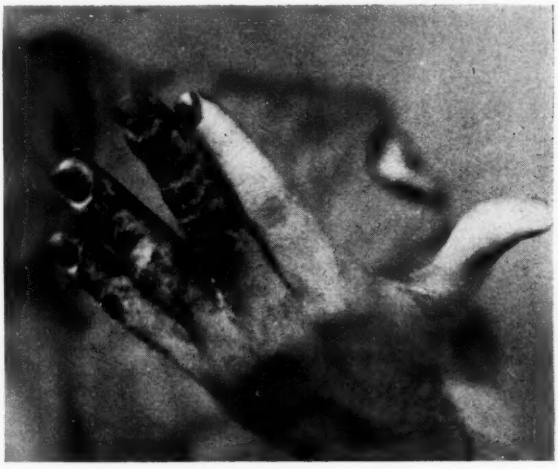

Fig. 12. Case 12. Dermatitis in central technician from handling a dental compound—"Coe-loid." Both hands are involved, the left hand being most affected.

secondary infection. Laboratory examinations, including complete blood studies, serological tests and urinalysis, were essentially negative. Smears from the skin lesions showed no fungi.

It was our impression that the patient had a contact dermatitis masked by the therapy which he had received and by the presence of the secondary infection. A solution consisting of five parts of boric acid and three parts of alum in five hundred parts of water was applied locally in compresses. His condition was so improved within a week that it was felt that a ten per cent boric acid ointment might complete the treatment. However, instead an exacerbation of the dermatitis occurred. Another exacerbation occurred when anhydrous lanolin was used. Recovery was finally effected by the use of a soothing lotion consisting of zinc oxide, talc, starch, bentonite, glycerin and water. During this patient's stay in the hospital, he was patch tested to sulfathiazole, petrolatum and lanolin. In each case positive reactions resulted. This soldier was returned to full duty and advised about the necessity of understanding the nature of his sensitivity. A recent communication from him states that he has remained in good health.

Case 7.—This twenty-six-year-old white soldier gave a history that since 1939 he had a recurring dermatitis during the summer. This dermatitis began with a few small pimples on his face and arms and finally resulted in a dermatitis all over his body, necessitating hospitalization. The condition would often persist well into the end of the summer season. Since his entrance into the service, the condition has continued to recur and because of it he has spent two sessions in different hospitals for prolonged periods of time. Each time he was given intensive treatment with poison ivy extracts.

His contact and allergic history prior to coming into the service had been positive, as evidenced by his statement that he had always had a very sensitive skin, especially when he went out into the country and was exposed to the various grasses and weeds.

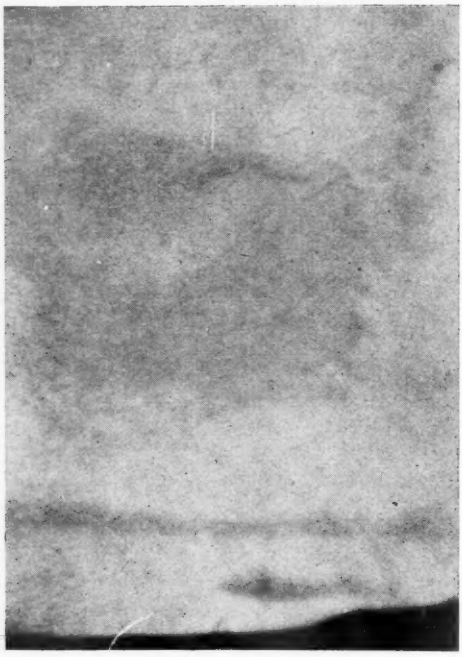

Fig. 13. Case 13. Dermatitis from money belt.

Physical examination, except for his dermatitis, was essentially negative. At the time of examination in May, he was beginning to have a dermatitis, most noticeable on his face, consisting of vesicles and papules which were very itchy. He stated that very soon this would become generalized, if it followed its previous course.

Laboratory examinations, including complete blood studies, serological tests and urinalysis were essentially negative.

It was our impression that we were dealing in this patient's case with a pollen dermatitis, rather than a poison ivy dermatitis, especially in view of the fact that poison ivy therapy failed to evoke a favorable response. Patch tests with the oily fractions of timothy and ragweed revealed moderately severe positive skin tests, as is shown on the photograph. Soothing therapy to the skin of his face prevented the condition from becoming more severe during the summer of 1943. An emulsion of timothy and ragweed pollen in sterile almond oil resulted in improvement and there were no additional generalized symptoms occurring during the remainder of the summer. At this time he is not under our care and we do not know of his

subsequent reactions. As reported in a previous article, this technique was successful in a severe case in private practice.[24]

Case 8.—A twenty-four-year-old white sergeant was transferred from the Fort

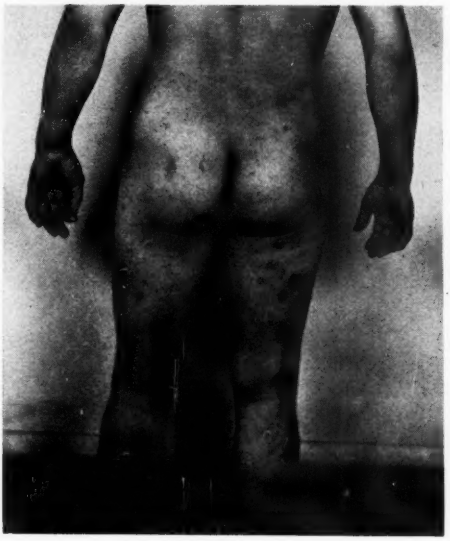

Fig. 14. Case 14. Dermatitis from toilet seat with secondary pyoderma.

Meyers Station Hospital in Florida where, he states, he first developed a skin eruption on his feet and legs. He was treated in the battalion dispensary in November of 1942 without improvement. He was then hospitalized for two months without improvement and was sent to Lovell General Hospital, from where he was discharged as cured and sent back to full duty. Because his dermatitis reappeared again after a few weeks on duty, he was returned to the Station Hospital in August, 1943, where he received sulfathiazole ointments, cod liver ointment and five x-ray treatments without improvement. He was then transferred to Oliver General Hospital 30 Steptember, 1943, for further study, treatment and disposition.

Contact and allergic history was negative, as was the remainder of his past history. Physical examination revealed essentially negative findings, except for the dermatitis of his feet and legs. The skin of the dorsum, ankles and lower third of both legs revealed encrusted areas with marked scaling and "oozing." The basic lesions were papules, pustules, crusts and scabs with fissures implanted upon an erythematous base. The pustules and crusting lesions were presumably the result of secondary infection. There were no apparent lesions between his toes or on the soles of his feet, although he had some small lesions of a pustular character on his hands, especially on the lateral aspects of his fingers.

Laboratory examinations, including complete blood studies and serological tests, were essentially negative. Smears from the skin lesions showed no fungi, but staphylococci were found. He did not react to trichophytin or oidiomycin skin tests intradermally.

It was our impression that the patient had a contact dermatitis masked by the therapy which he had received and by the presence of secondary infection. Potassium permanganate in a 1-5000 dilution was used at the outset with poor results. The area involving his lower extremities was then treated with three

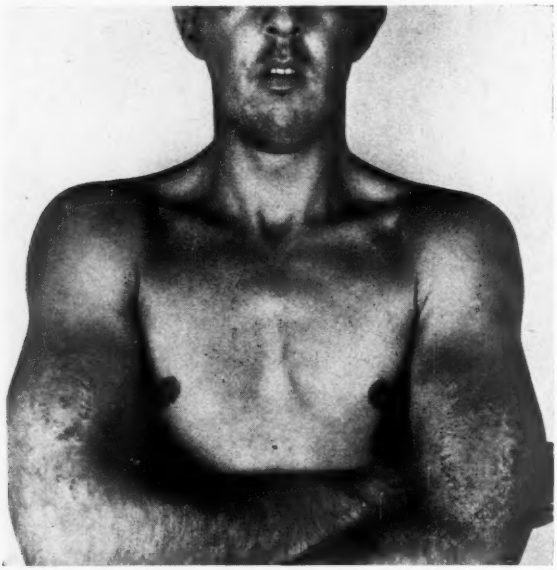

Fig. 15. Case 15. Dermatitis on outer aspects of the middle of the arms. Note vesicular character of lesions. Dye in chevrons proved to be contactant responsible.

per cent sulfathiazole in an aqueous lotion consisting of zinc oxide, starch, bentonite, and glycerin. Poor results were obtained. The condition continued to be troublesome, drying up partially at times, then again breaking down.

In view of the chronicity of this condition and the finding of positive patch test reactions to GI wool socks and O.D. material, and in the absence of a reaction to undyed wool, it was our opinion that this soldier was suffering from a dye dermatitis complicated by secondary infection. Inasmuch as he was not wearing his dyed socks or wool O.D.s at this time, the important problem here was to correct the persistent infection. Plaster casts were applied to both legs and feet for the purpose of avoiding further irritation of his skin by scratching and for the possibility of healing by bacteriophage action. These casts were kept on his extremities for one month, during which time a very pronounced odor developed, so that the casts were removed. The improvement of his legs was so advanced, that mild local applications of boric acid solution with alum, as described above, completely cleared up the condition. This patient was then returned to full duty, with instructions that he wear nothing but undyed socks. No report as to the ultimate outcome or recurrence is known at this time.

Case 12.—A twenty-six-year-old white corporal developed a dermatitis about April of 1943. It started as small blisters on the thenar eminences of both hands. The condition would dry, recur and finally spread to the fingers. This was as-

Fig. 16. Case 16. Dermatitis from camphor-phenol eutexia superimposed on an existing contact leather dermatitis, previously diagnosed and treated as tricophytosis.

Fig. 17. Case 17. Dermatitis from gasoline in crew member of B-25, who was plane mechanic.

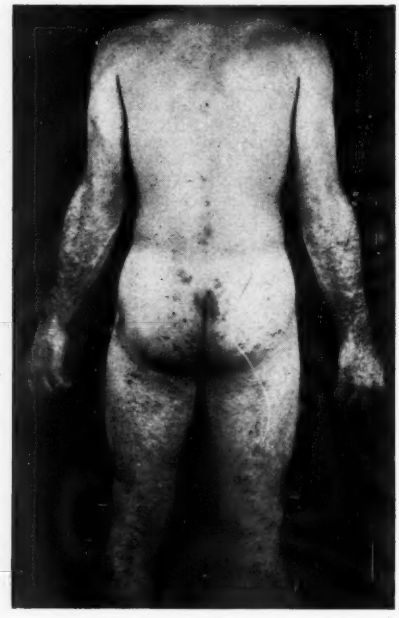

Fig. 18. Case 18. Dermatitis from a soap highly advertised for B.O.

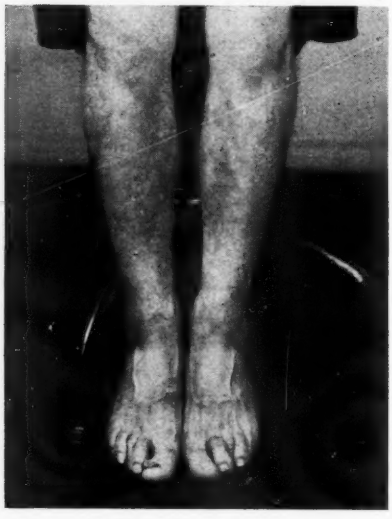

Fig. 19. Case 19. Dermatitis of legs from dye in trousers. There was no apparent sensitivity to the material.

sociated with mild itching at the outset, and later in the course of the condition the itching became marked. He had many types of local treatment, including light therapy, which helped his dermatitis to dry up, but he often found that following the use of soap and water the condition would flare up. The soldier stated that the

Fig. 20. Case 20. Dermatitis from cutting oil used in the operating of machine tools; secondary pyodermatitis was present. Distribution was symmetrical, extensor surfaces of both forearms being involved. Facticial element was strongly suspected.

dermatitis first seemed to appear after he began to use an impression compound known as "Coe-loid," while he was working in the dental clinic as an assistant. In the previous six weeks he had had no contact with this impression compound, and the irritability of his hands seemed to be quieting down.

Contact and allergic personal history was negative, but he stated that his mother had hay fever. His remaining past history was negative. Physical examination, except for the dermatitis, was negative. Over the skin of the hands, bilaterally involving principally the fingers of both hands, most markedly on his left hand, he presented a profuse eruption in several stages. Superimposed upon an erythema-

tous base there were pustules and vesicles with marked desquamation, cracking and fissuring of the skin of his fingers and considerable stiffening of his fingers from disuse.

Fig. 21. Case 21. Dermatitis involving popliteal space and a large part of thigh and leg of but one lower extremity in an asthmatic of recent occurrence and negative atopic history. Elastic knee support was contactant involved.

Laboratory examinations, including complete blood studies, serological studies and urinalysis, were essentially negative.

He gave a moderate reaction to Coe-loid dental compound as well as slight reactions by intradermal testing to asparagus, sweet potatoes, tomatoes and radishes. The various skin tests were accomplished because of a mild vasomotor rhinitis of which he complained and which examination verified. It was our opinion that the patient had an interesting skin condition probably due originally to intimate contact with this dental compound, with superimposed secondary infection. The superimposed secondary infection was cleared up first by the use of soothing medication consisting at first of a potassium permanganate solution of a 1-5000 strength for one week, followed by the use of a zinc oxide, starch, bentonite, glycerin and water solution, and subsequently, massage to his fingers. The best treatment for a contact dermatitis of this type is avoidance. Where avoidance is not possible, rubber gloves may be tried. In this case, the soldier was returned to duty with a recommendation for reassignment where he would not be required to handle the offending contactant.

Case 15.—A twenty-five-year-old white Staff Sergeant was admitted to Oliver General Hospital in August, 1943, with a dermatitis involving the outer aspects of both arms. He stated that during the previous hospitalization his condition had

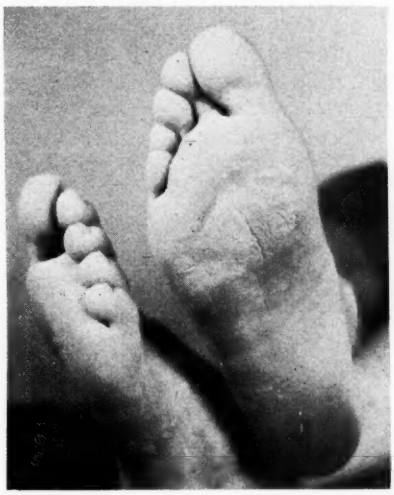

Fig. 22. Case 22. Dermatitis from arch supports worn inside shoes, secondary to subacute epidermophytosis and marked hyperidrosis.

improved somewhat under the various types of medication which had been applied, but that the lesions recurred quite regularly. He could give no clues as to the cause other than the fact that he had to report on sick call frequently for a local type of medication because of the recurrence of the blisters and the severity of the discomfort.

Contact and allergic history was negative, except for a history of occasional dermatitis from poison ivy. This dermatitis was always mild; therefore, he never took any medication for it. The remainder of his past history was negative. Physical examination, except for his dermatitis, was found to be negative. Limited to the skin of both arms, involving the lateral aspects of the mid-portion of the arms, was a moderately severe dermatitis showing a macular, papular, vesicular eruption on a mild erythematous base, with some desquamation, scaling and crusting.

Laboratory examinations, including complete blood studies, serological tests and urinalysis, were essentially negative. A smear from the lesions was negative for fungi.

Patch tests to the clothing, including socks and khakies, were negative, as were the reactions to leather and various chemicals. However, it occurred to us, because of the unusual distribution of the lesions, that this might be a dye dermatitis produced from the dyed portion of the cloth to which his chevrons were sewn. A portion of this dyed material was used in patch testing and to this he gave a moderate to marked reaction. On the basis of this positive finding, it was our opinion that we were dealing with a contact dermatitis. After local treatment with boric acid and alum compresses for approximately one week,

followed by soothing, protecting lotions containing zinc oxide, starch, bentonite, talc, glycerin and water, the condition completely cleared. The soldier was advised to wear long-sleeved underclothes for protection, and, if necessary, two undershirts. This soldier was returned to duty.

Fig. 23. Case 23. Dermatitis from bichloride of mercury solution used in a case of pediculosis. Note marked edema of scrotum. Itching was intense.

Case 16.—A twenty-two-year-old white soldier was admitted to Oliver General Hospital 18 September 1943 with a dermatitis involving both feet. In eighteen months of service, this was his fourth admission to an army hospital. His most recent admission was at Daniel Field Station Hospital 10 July, 1943, where he remained for approximately seven weeks prior to his admission here. This patient had had various medications applied to his feet, including a five per cent solution of alum, gentian violet, and Castellani's solution, and a heat lamp was used. In addition, he heard about the use of camphor-phenol eutexia in the treatment of athlete's foot, and he used it, thinking it would cure his condition, since it was his impression that he had a severe case of athlete's foot.

Contact and allergic history was negative except for a history of athlete's foot of four years duration. The remainder of his past history was negative.

Physical examination, except for his dermatitis, was essentially negative. Over the skin of both feet, involving the big toe and especially the second and third toes, bilaterally, and over the insteps of his feet, occurred a marked amount of crusting, "oozing," vesiculation, papules and pustules with a moderate amount of pigmentation. The lesions about his toes were of a more acute nature, since they appeared to be planted upon an acute erythematous base. From his history, it was apparent that this was where he had applied the camphor-phenol medication.

Laboratory examinations, including complete blood studies, serological tests and urinalysis, were essentially negative. Smears from the skin lesions on several occasions showed no fungi.

Trichophytin reaction by intradermal and patch tests was negative. However, he reacted very markedly to a piece of leather from his GI shoes as well as to

a 0.005 solution of sodium dichromate. It was our impression that we were dealing with a contact dermatitis due to leather, upon which was superimposed a dermatitis produced by camphor-phenol. Trichophytosis was ruled out by the absence of any fungi between the toes. Local treatment consisted of soaks of

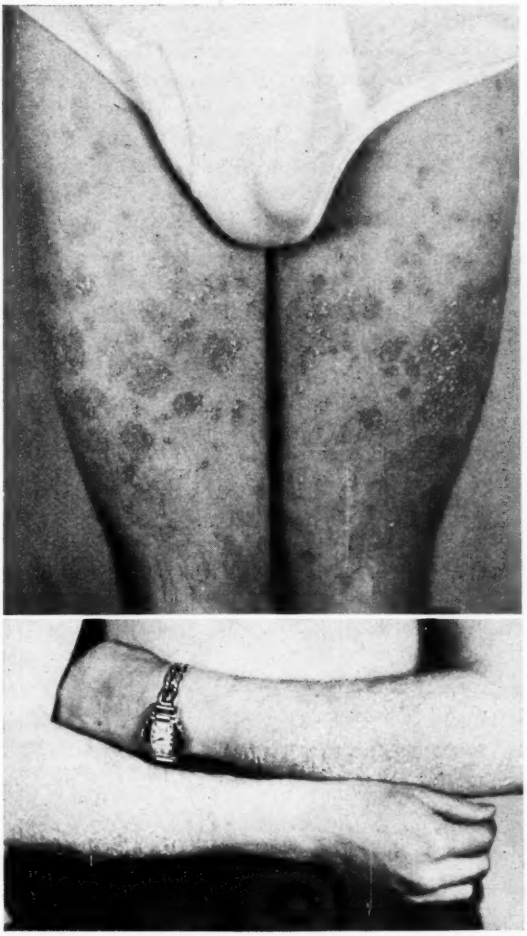

Fig. 24. Case 24. Contact dermatitis, due to wool and O.D. wool clothing, as proved by patch tests to a segment of the patient's own wool clothing and a patch of undyed wool.

potassium permanganate, 1-5000 solutions, three times daily for one week, followed by twice daily soaks of boric acid and alum solution for five days, after which no therapy was used. The condition of his feet cleared and a trial at wearing his GI shoes was made. Within twenty-four hours, he developed marked itching

and vesiculation on the insteps of his feet, which subsided after the avoidance of wearing the shoes. The wearing of low-quartered shoes resulted in less discomfort, but did not completely eliminate the condition. It was felt that separation from the service in this case was indicated, and it was accomplished.

Since this article was originally written, antibiotics such as penicillin, streptomycin and others to come are being widely used at the present moment in the treatment of numerous diseases, both parenterally and locally. Contact with the antibiotics whether because of treatment or through the handling of such material, has caused moderate to severe reactions on the skin as illustrated by the reports of Robinson and Wallace[27], Johnson[17], Pyle and Rattner[25], Raper and Coghill[26], and McGuire.[20] Nurses, technicians, corpsmen and WACs have had reactions on their extremities and face following the preparation of penicillin for treatment purposes. In some of these individuals, their reactions have occurred within six to eight hours after contact with penicillin.

Capt. Lawrence C. Goldberg[12], Chief of Dermatology at Oliver General Hospital, stated that, in his experience, "some 6 to 8 per cent of the individuals treated with topical applications of penicillin, where 800 units of penicillin was used per gram of vehicle, demonstrated mild to severe local reactions. Sixteen cases of dermatitis venenata caused by penicillin or its impurities have been proven by patch tests. Occasionally the parenteral or local use of penicillin in the treatment of skin diseases will produce a localized Herxheimer reaction, which must be differentiated from a contact dermatitis. This type of reaction usually subsides within forty-eight hours and appears to be the result of impurities rather than the penicillin itself." The sites of predilection for contact dermatitis from penicillin when caused by the preparation of the drug may be on other portions of the body other than the fingers and hands so that it should be suspected in medical attendants and workers who complain of facial pruritus and orbicular edema.

A clinical example of penicillin dermatitis is described.

B. F., 2nd Lt., ANC, appeared in consultation at the Dermatology Out Patient Clinic on 15 December 1945 because of erythema and edema of the right eyelid associated with erythematous macules on the face. Pinhead sized vesicles were present on the forehead, nose, and perioral areas. She stated that itching and swelling of the face first was noticed on 10 December, 1945. A diagnosis of contact dermatitis was made and the patient was hospitalized. In three days after local treatment with cold wet dressings of Burow's solution, the eruption and the edema subsided and the patient was returned to duty. At that time, the cause of the dermatitis was unknown. Within forty-eight hours, the patient reappeared for consultation because of severe edema of the eyelids, nose, and lips and a recurrent erythema of the face. It was learned that during this time she had been preparing and administering intramuscular injections of penicillin in 20,000 units per c.c. quantities and it appeared that after each injection given to a patient, itching and edema of her face increased. She was again relieved of duty and hospitalized. Treatment as before cleared the condition within three to four days. A patch test with penicillin, 250 units per c.c., was made on the flexor surface of the right forearm and within

forty-eight hours a 3 plus reaction was noted. After a ten-day leave, the patient returned to duty and a test dose of penicillin was prepared, 250 units per c.c., and injected into a patient. Shortly thereafter, slight swelling and itching of the eyelids and face were noted.

The interesting observation on this particular patient was the fact that the entire contact dermatitis appeared on the face but never involved the extremities or any other portion of the body. In many respects, this type of reaction is similar to that seen in nail polish dermatitis.

SUMMARY

The use of the term contact dermatitis in this paper has been broadly interpreted and includes that group of acute or chronic inflammatory reactions in the skin, often called dermatitis venenata, eczematous dermatitis, or just eczema. It is a type of dermatitis involving chiefly the epidermis and is the result of contact with external agents. It is characterized by a vesicular eruption on the exposed surfaces of the skin at the outset of the dermatitis.

Contact dermatitis is a frequent cause of morbidity in the army, because it is known to be more common in adult males, who are more likely to be exposed to contact with external irritants. The contactants which may produce contact dermatitis are legion—they may be drugs, clothing, dyes, metals, chemicals, paints, lacquers, or they may be cosmetics (orris root), insect powders (pyrethrum) or many other items. They may be plants, such as poison ivy, oak, sumac, anacardiacea, timothy, or ragweed. In these instances the contactant is an oleoresinous substance present in the leaf of the plant or in the pollen. From a clinical-pathological standpoint, the eruption occurs after a period of previous exposure to the irritant. This contact may occur with large quantities of the excitant, causing symptoms. Once the sensitivity has been produced, however, contact dermatitis may result from infinitesimal amounts. The location of the dermatitis is of diagnostic significance, since it may point to the possible cause. Diagnosis is further aided by a careful history. Final proof of the cause is established by the patch test which requires proper interpretation. Cure will depend on complete removal of the contact and the disappearance of the eruption, except when complicating secondary infection is present.

Pathologically, the anatomic lesion of contact dermatitis is an edema of the epidermis, which is responsible for the typical vesicle. Since this is the result of specific sensitivity in the superficial layer of skin, the necessity for placing the excitant to be tested in direct contact with the skin is thus explained.

Since the lesions of contact dermatitis generally involve the exposed surfaces of the body as a result of contact with external excitants, the presence of vesicles and the absence of a personal or family history of atopy

make the differential diagnosis of contact dermatitis from atopic eczema fairly definite.

The treatment and disposition of contact dermatitis depend upon finding the specific cause. If this has been accurately determined, the only effective cure is, in most cases, the avoidance of contact. This is not always practical in the case of soldiers sensitive to their uniforms or shoes. In some instances, protection can be had by the use of long underwear, but this may not be adequate to avoid skin reactions. Desensitization cannot be carried out against many chemicals and articles of clothing in the army where avoidance cannot be practiced, so that the only expedient thing to do, in many cases, both from the standpoint of the government and the patient, is separation from the service.

Specific desensitization can be used with success only in types of dermatitis produced by plants and pollens, as for example, poison ivy plant and ragweed pollen. Treatment may be administered as prophylaxis or in active treatment when the attack of plant or pollen dermatitis has occurred.

Finally, it must be remembered that we are frequently dealing with an uncomfortable patient who requires relief, so that local applications of soothing, aqueous, anti-pruritic and mildly astringent lotions should be employed in the acute cases. Ointments, X-ray and ultraviolet light therapy may be beneficial in the chronic types as palliative measures. Vaccines, histamine or other non-specific measures are of less value in dermatitis due to contact than in the atopic dermatoses.

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(Continued on Page 141)

PRELIMINARY PROGRAM

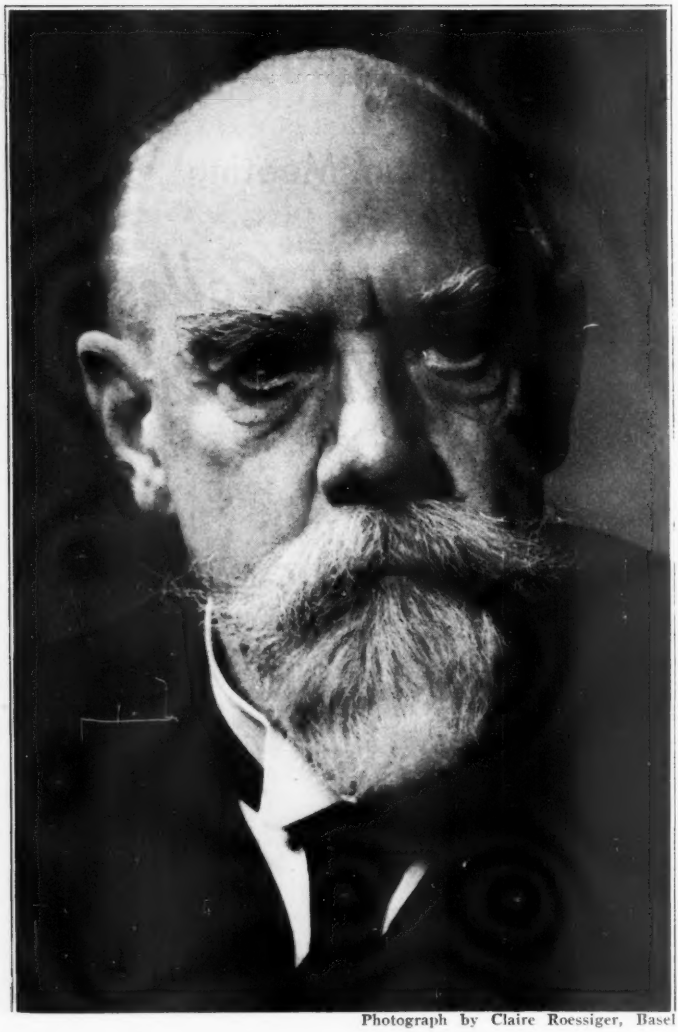
Annual Meeting

American College of Allergists

June 28-30, 1946
Clift Hotel
San Francisco, California

96th Annual Meeting, American Medical Association, St. Francis Hotel, San Francisco, July 1-5, 1946.
12th Annual Meeting, American College of Chest Physicians, Hotel Sir Francis Drake, San Francisco, June 27-30, 1946.

NOTE: The papers will not necessarily be presented in the order indicated in this preliminary program and the titles of the papers and authors are subject to change.



Photograph by Claire Roessiger, Basel

ROBERT DOERR, M.D., Ph.D.

Professor Emeritus of Hygiene and Bacteriology at the University of Basel, Switzerland

Guest Speaker, 1946

Preliminary Program

Friday, June 28, 1946

Breakfast

Clift Hotel—7:30 to 8:30 a.m.
Members of Board of Regents and Program Committee

Registration

Roof Lounge—8:00 a.m.

Morning Session

Roof Lounge—9:00 a.m.
RUDOLF L. BAER, M.D., *Chairman*

Experimental Sensitization and Antihistaminic Substances—R. L. MAYER, M.D., Summit, New Jersey
Evaluation of Intramuscular Injections of Poison Ivy Extract for the Treatment of Acute Rhus Dermatitis—J. B. HOWELL, M.D., Dallas, Texas
Contact Testing of the Buccal Mucous Membrane with Special Reference to Penicillin—LEON GOLDMAN, M.D., Cincinnati, Ohio.
Urticaria Due to Handling of Penicillin and Sulfa Drugs—KATHARINE BAYLIS MACINNIS, M.D., Columbia, South Carolina
Relationship of Antihistaminic Drugs to Other Forms of Therapy in Nasal Allergy and Asthma—ALBERT V. STOESSER, M.D., Minneapolis, Minnesota
Benadryl in the Treatment of Certain of the Allergic Diseases of Childhood—GEORGE B. LOGAN, M.D., Rochester, Minnesota
Food Allergy: A Clinical Problem—ORVAL R. WITHERS, M.D., Kansas City, Missouri

College Luncheon

Clift Hotel—12:30 to 2:00 p.m.

Afternoon Session

Roof Lounge—2:00 p.m.

PAN-AMERICAN CONGRESS ON ALLERGY
INTERNATIONAL ASSOCIATION OF ALLERGISTS

FRED W. WITTICH, M.D., *Chairman*

Introduction of ROBERT DOERR, M.D., Ph.D., Basel, Switzerland, Guest Speaker Saturday morning session.
Opening Address, "Terminology and Classification of Allergy"—GUIDO RUIZ-MORENO, Buenos Aires, Argentina; Argentine Allergy Society
The Influence of the Liver on Anaphylactic Shock in the Dog—ALFONSO GRAÑA, M.D., Montevideo, Uruguay
Topic to be announced—G. ESTRADA DE LA RIVA, M.D., Havana, Cuba
Topic to be announced—FRANCISCO J. FARRERONS, M.D., Barcelona, Spain
Topic to be announced—MARIO MIRANDA, M.D., NELSON PASSARELLI, M.D., Rio de Janeiro, Brazil.
Topic to be announced—Representative from Canada
Clinical and Physical Nature of Pollen Allergens—HAROLD ABRAMSON, M.D., New York, N. Y.

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Evening Session

Roof Lounge—8:00 p.m.

THE ASSOCIATION OF ALLERGISTS FOR MYCOLOGICAL INVESTIGATION

Symposium on Mold Allergy

HOMER E. PRINCE, M.D., Houston, Texas, *Director*

Mold Allergy in West Texas—
Clinical Observations
ERLE D. SELLERS, M.D.
Discussion opened by: ORVAL WITHERS, M.D., Kansas City, Missouri

Mold Fungi in the Etiology of Respiratory Allergic Disease
A Survey of Air-borne Fungi in the San Antonio Area, and a Correlation with Skin Reactions to Mold Extract
STANLEY F. HAMPTON, M.D.
Discussion opened by: PEARL ZINK, M.D., San Antonio, Texas

Mold Fungi in the Etiology of Respiratory Allergic Disease:
Further Survey Studies in Various Cities
MARIE B. MORROW, Ph.D., Austin, Texas
Discussion opened by: MERLE MOORE, M.D., Portland, Oregon

Intrinsic Fungus Problems in Relation to Asthma and Bronchitis:
L. O. DUTTON, M.D., El Paso, Texas
Discussion opened by: FRED WITTICH, M.D., Minneapolis, Minnesota.

Saturday, June 29, 1946

Breakfast

Clift Hotel—7:30 to 8:30 a.m.
Members of Board of Regents and Program Committee

Registration

Roof Lounge—8:00 a.m.

Morning Session

Roof Lounge—9:00 a.m.
HARRY L. ROGERS, M.D., *Chairman*

Address of the Guest of Honor—Integration and Differentiation of Allergic Phenomena—ROBERT DOERR, M.D., Ph.D., Professor Emeritus of Hygiene and Bacteriology at the University of Basel, Switzerland.

Reagins: Preliminary Report on Experimental Evidence in Support of a New Theory of their Nature—HYMAN MILLER, M.D., Beverly Hills, California, and DAN CAMPBELL, Ph.D., California Institute of Technology

Food Allergy in Dogs—RALPH POVAR, M.D., Rhode Island

Contact Dermatitis in the Horse—LESTER REDDIN, JR., V.M.D., Pearl River, N. Y.

Allergy and Immunity to Crystalline Insulin—MARY H. LOVELESS, M.D., New York, N. Y.

Quantitative Relationships in Anaphylaxis and Allergy—ALFRED J. WEIL, M.D., Pearl River, N. Y.

Inhalant Allergens in Southern California—WILLARD S. SMALL, M.D., Pasadena, California

College Luncheon

Clift Hotel—12:30 to 2:00 p.m.

PRELIMINARY PROGRAM

Afternoon Session

Roof Lounge—2:00 p.m.
MERLE W. MOORE, M.D., *Chairman*

Aerosol Therapy of the Lungs and Bronchi—HAROLD ABRAMSON, M.D, New York, N. Y.

Recent Developments in the Treatment of Intractable Bronchial Asthma (including moving picture demonstrations)—ALVAN L. BARACH, M.D., New York, N. Y.

Mistakes in the Treatment of Asthma—GEORGE WALDBOTT, M.D., Detroit, Michigan

Continuous Intravenous Aminophyllin Therapy in Status Asthmaticus—ROBERT J. GOODALL, M.D., Chicago, Illinois and LEON UNGER, M.D., Chicago, Illinois

Grass Pollen Counts of the Los Angeles Area—A. M. TARGOW, M.D., Los Angeles, California

Allergenic Potency of Pollen Extracts: Technical Considerations—ROGER P. WODEHOUSE, Ph.D., Pearl River, N. Y.

Respiratory Mold Allergy—A Twelve Months' Atmospheric Survey in San Francisco —WILLIAM C. DEAMER, M.D., San Francisco, California

Cocktail Hour

Clift Hotel—6:15 p.m. to 7:15 p.m.
Presented through the courtesy of
Frederick Stearns and Company, Detroit, Michigan

Informal Dinner

Clift Hotel—7:15 p.m.

Sunday, June 30, 1946

Breakfast

Clift Hotel—7:30 to 8:30 a.m.
Members of the Board of Regents and Program Committee

Registration

Roof Lounge—8:00 a.m.

Morning Session

Roof Lounge—9:00 a.m.
FRENCH K. HANSEL, M.D., *Chairman*

Some Properties of Antigens and Antibodies—SANFORD B. HOOKER, M.D., Boston, Massachusetts

Application of Peroxide Solutions to Allergic Syndromes—ETHAN ALLAN BROWN, M.D., Boston, Massachusetts

Use of the Sex Hormones in Allergic Disorders—MILTON M. HARTMAN, M.D., San Francisco, California

Histamine and Deafness—BAYARD T. HORTON, M.D., and OLAV E. HALLBERG, M.D., Rochester, Minnesota

Psychoanalysis and Psychosomatic Allergy—COYNE H. CAMPBELL, M.D., Oklahoma City, Oklahoma

PRELIMINARY PROGRAM

College Luncheon

Clift Hotel—12:30 to 2:00 p.m.

Afternoon Session

Roof Lounge—2:00 p.m.

HAL DAVISON, M.D., *Chairman*

Vascular Allergy—JOSEPH HARKAVY, M.D., New York, N. Y.

3:30 p.m.—Presidential Address—HARRY L. ROGERS, M.D., Philadelphia, Pa.

4:00 p.m.—Annual Business Meeting.

Important Announcement

There will be a meeting of the Board of Regents of the College, Thursday, 2:00 P.M., June 27, at the Clift Hotel, San Francisco.

There will also be an important meeting of the Standardization Committee, Thursday evening, June 27, at 8:15 P.M., at the Clift Hotel. See Page x for those on this Committee. All members of the Board of Regents are also urged to attend.

ANTIGENICITY OF PROTEINS IN RELATION TO ALLERGY

WILLIAM H. WELKER, Ph.D., Sc.D.

Chicago, Illinois

I appreciate the invitation to speak before this group. It must be understood, however, my interests do not lie in the field of allergy from the standpoint of the practice of allergy. I have been interested for many years in the chemistry of proteins and through my collaboration with Dr. Hektoen I became interested in their immunologic reactions. I wish to acknowledge my indebtedness to Dr. Hektoen for the development of my appreciation of this angle of the protein knowledge. I also wish to acknowledge my indebtedness to many young medical students whose scientific curiosity stimulated them to carry out work which supplied much of the information that we have on this subject at the present time.

The immunology of proteins is today much confused because most of our present information has been secured with mixtures of antigens, such as blood sera, bacterial filtrates and other material of the same type. Such mixtures contain many antigenic entities, diversified in character and as a result the interpretation of their effects is beyond the capacity of the human mind.

Twenty years ago, in his book on The Chemical Aspects of Immunity, Wells[14] made the following statement (he is speaking about the results obtained on protein cleavage products): "These are variable preparations concerning the source, composition, and the purity of which the observer has no knowledge. To call work done with such materials scientific investigation is in my conviction a prostitution of the word science, a parody of its standards and ideals." This statement in my judgment applies with equal force to the use of mixtures of antigens, known and unknown, in studies to establish antigenic effect. Later in his text he makes the following statements in italics: "The fundamental processes of immunity should be studied only with the simple antigens of known composition, i.e., isolated pure protein."[14] For those who are interested in the fundamental science I would recommend the reading and study of this book.

When we study the antigenicity of a protein we shall have to take into consideration not only the reactivity of the protein itself, but also the reactivity of the species. Not all species have the ability to react with proteins that are known to be highly antigenic to some species. In our present state of knowledge we know of three classes of antigens. These groups differ from the chemical standpoint in size of the molecule and

From the Department of Biological Chemistry, University of Illinois, College of Medicine, Chicago, Illinois. Delivered at the dinner given by the American College of Allergists, at the instructional course held in Chicago, Illinois, November 5, 1945.

from the physical-chemical standpoint in the size of the particle in solution. The response of the reactive animal organism is different in the case of each of these groups. It is my belief that the difference in the response to these three classes of antigens is due largely to the particle size of the protein when in solution. In all probability, different cells of the animal organism are called upon to handle them when they appear in the blood stream and the different groups of cells have their own characteristic methods for handling the situation.

When diluted egg white (1 per cent protein in physiological salt) is injected into the blood stream of the dog, the reticulo-endothelial system becomes engorged with the large particles and relatively small doses will cause death.[12] If these same proteins are injected in a more highly dispersed solution, the kidney can handle large quantities of them readily.

The first group of antigens consists of antigenic proteins of relatively large molecular size. An example of this group is ovalbumin. When these proteins get into the blood stream of a responsive animal they will cause the production of antibodies of the type of precipitins, agglutinins, lysins, et cetera. They also have the power of producing anaphylactic sensitivity. It has been unfortunate for the progress of our basic conceptions in allergy that our train of thought has been developed along the lines of anaphylaxis or anaphylactic sensitization. This type of antigen does not readily produce a response in the human organism. If it did, the use of antitoxins would become extremely hazardous. There is the possibility that the human organism may develop anaphylactic sensitivity to the pseudoglobulin of the horse which is the main constituent in diphtheria and tetanus antitoxin, but such development is so rare that there are few practicing physicians who make use of any precautionary methods in connection with the use of these two antitoxins.

C. W. Wells[13] studied the blood of diphtheria patients who had been treated with whole horse serum diphtheria antitoxin. Out of 26 cases studied one showed a titer of over 1-40,000, four over 1-20,000 and one over 1-10,000, the rest inconsequential or negative. Tuft and Ramsdell[10,11] carried out work along the same lines on the human subject and found even less response. Coca[5] used normal subjects and normal horse serum and obtained negative results.

The rabbit and guinea pig show a very high degree of response to this class of antigens. A precipitin titer of 1-100,000 or 1-1,000,000 is common. When the human organism is in a pathological state, conditions may exist which favor the formation of precipitins to an antigenic protein. After the epidemic of typhoid fever at Manteno, Spinka[12] studied the blood of all the recovered cases and found that all of them had high precipitin titers for the characteristic protein of the typhoid organism. The diphtheria cases studied by C. W. Wells were all in a toxic state due to the fact that they were suffering from diphtheria which may account

for the response obtained in his series. Tuft and Ramsdell used individuals that were treated with antisera for specific infections and the few positive responses that were observed by them can well have been due to the conditions produced by the pathologic state.

Coca used normal individuals and normal horse serum and obtained negative results. He interpreted his results as due to the fact that he had used normal horse serum while Tuft and Ramsdell had used antitoxin horse serum. I am inclined to believe that the differences in the results obtained were due to the fact that Tuft and Ramsdell had used sick individuals while Coca's subjects were normal. This is further borne out by Burky's[3] experiments on the production of sensitivity to the lens protein of the rabbit in the rabbit. This sensitivity could not be produced without the simultaneous injection of staphylococcus toxin. The generally accepted explanation of these results is that the toxin forms a compound with the lens protein and the sensitivity is produced by the foreign protein compound so formed. It might be possible, however, that the toxic condition produced in the rabbit favored the precipitin formation. In the dog, L. Mann and Welker[12] and other investigators have been unable to induce any precipitin formation for antigenic proteins injected. The staphylococcus toxin will not aid in the precipitin formation in this species. It should however, combine with the antigen and thus favor precipitin formation. It also fails to produce any toxicity in the dog. Toxic conditions produced by other means make it possible to produce precipitins in the dog.

An antigenic large protein molecule in animals that have the ability to respond will produce precipitins. In species that normally do not produce these antibodies, the antigenic large protein molecule may produce precipitins under abnormal conditions. These antigenic large protein molecules apparently do not have the power of producing any skin reactivity. A human case of egg sensitivity was studied in the following manner by Aaronson and Cole.[1] The first crystallization of ovalbumin produced a good skin reaction in an egg-sensitive case. Successive crystallization of the same ovalbumin showed diminishing reactions and at the point of the seventh crystallization the skin reaction had disappeared. The precipitinogenic power of this preparation showed no diminution on successive crystallizations. It is, therefore, logical to assume that pure crystallized ovalbumin has no skin reactivity.

The work of Roth and Nelson[9] on pollen, using successive extractions of pollen, showed that after a certain number of extractions all skin reactivity was absent from subsequent extracts. The precipitinogenic power was still present in these later extracts, indicating that the large protein molecule at this point had been freed from the skin reacting substances but its original chemical nature had not been altered. The precipitinogenic power was tested on pollen antisera prepared in the rabbit.

Rappaport and Levin[5] studied this problem by dialyzing a pollen solution against frequent changes of distilled water. They studied the skin reactivity in known pollen-sensitive cases of the solution in the bag on the basis of the nitrogen content and found that the skin reactivity diminished and finally disappeared. They are not entirely satisfied and expect to repeat the work before final publication. The proteins that belong to this group in solution at or near their isoelectric point will not diffuse through permeable membranes.

The next group of antigens consists of proteins of smaller molecular size, typified by the bacterial toxins. These do not form precipitins but form neutralizing antibodies. They will slowly diffuse through permeable membranes and they produce delayed skin reactions. The particle size of the toxin in solution by virtue of its ability to pass through permeable membrane is smaller than that of the particle size of the antigens of the first group.

Here again the question of ability of a given species to respond to the antigens is worth while considering. When it was found that the rabbit produced an antipneumococcus serum that was valuable in the treatment of pneumonia, Dr. Jamieson[7], Director of the Biological Division of Eli Lilly and Company, studied the ability of the rabbit to produce diphtheria antitoxin. The highest titer obtained in the rabbit after immunization with diphtheria toxin was 4 units per c.c., showing a very marked difference in the degree of responsiveness to this antigen of the rabbit as compared to that of the horse. The preparation of antitoxin antiserum is not practical in the rabbit since the response of this species is feeble to this class of antigens. The pneumococcus antiserum prepared in the the horse was of no particular value. The effective agent in the rabbit antipneumococcus serum is the precipitin antibody. The horse is not capable of readily preparing precipitins.

Through the work of Benjamins[2] and his collaborators on grass pollens and of Hecht, Rappaport and Welker[6], we are introduced to the third group of antigens. This is the group of antigenic substances which I believe is responsible for all forms of allergy. Its particle size in solution is smaller than that of the toxins. It dialyzes readily through a permeable membrane. In nature it occurs partially in combination in form of surface compounds with the larger protein molecule. That is why preparations of the large protein molecule from food and environmental material may show positive skin reactions in sensitized individuals. It is interesting that such small molecules should be as specific as they appear to be. It has been shown that this small molecule can be prepared free from any of the large molecules. This small molecule is exquisitely skin reactive. When completely freed from the large molecule pollen it will not produce precipitins and it will not produce anaphylactic sensitivity. Since this molecule is so small and so readily diffusible, it is apparent that these allergy anti-

gens must be present in the blood stream of all individuals who are exposed to environmental antigens or food allergy antigens. Our old theory of accidental introductions of these antigens into the blood stream as the reason for production of sensitivity is no longer valid.

Through the work of Coca[4], we now know that those individuals react to the presence of these antigens only because the allergic individual has developed a response called reagin. We know nothing about the conditions under which the reagin develops. The human organisms must have resistance against the development of the reagin, otherwise we should be one hundred per cent allergic. The reagin, according to Coca[5], is different from the precipitin antibody and also from the anaphylactic sensitizing antibody. The allergy problem deserves study, divorced from concepts that are based on information derived from the use of antigens that are entirely different from those involved in allergy.

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Author's comment: "On first glance the results cited might be interpreted as an indication that penicillium-sensitive persons are definitely safe from allergic reactions to penicillin. However, certain quantitative factors must be considered. A probably safe dose of the penicillium extract would be 1,000 times the minimal amount (0.02 c.c. of 1,000) required to give a skin test. On the other hand, a normal daily therapeutic administration of penicillin would be about 200,000 units, or 20,000 times the maximum dose (0.02 c.c. of 500 units per c.c.) used in our tests. This fact, coupled with the greater likelihood of systemic allergic reactions from intravenous administration, makes it impossible to say at the present time that the probability of allergic reactions can be totally ignored. The answer to this question will be more clear when purer and nonirritating penicillin products will be available or when actual therapeutic doses will be administered to penicillium-sensitive persons. Because also the original source of penicillin is a potent antigen and conceivably at times some of the antigen may be a final contaminant, it is suggested that as an added safeguard every batch of commercial penicillin be tested on known penicillium-sensitive individuals."

D.H.E.45 (DIHYDROERGOTAMINE) IN THE TREATMENT OF ALLERGIC MIGRAINE

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HEADACHE represents one of the most common complaints. Although extensive studies have been in progress in an effort to evaluate the causative factors, the patient's chief concern is to seek symptomatic relief from migrainous headache which is so frequently incapacitating.

Many hypotheses have been advanced, but the etiology of migraine still remains unsolved. The mechanism of migraine is believed to be due to a vasoconstriction followed by a vasodilatation of the cerebral arteries. The vasoconstriction produces the aura, scotomata and other phenomena and the vasodilatation produces the headache by stretching the pain fibers closely associated with these arteries. There is disagreement on the trigger mechanism that first causes the vasoconstriction and the vasodilatation that follows. One of the accepted theories is that migraine is an allergic reaction. Von Storch[6] reported a considerable number of migrainous patients as allergic. Rowe[5] reported only 17 per cent failure by the use of elimination diets.

In recent years ergotamine tartrate has been found to be the drug of choice in the treatment of typical migraine. Although the mechanism of action of this drug is still unknown, nevertheless the drug has been found to be useful in aborting headaches due to various causes. Lennox and Von Storch[4] report that 90 per cent of the patients obtained prompt relief when ergotamine was given intravenously or subcutaneously. One of the undesirable features of ergotamine is the production in some cases of nausea, vomiting and precordial pain. However, these side effects can be diminished by giving a minimum effective dose and it can be said that once a headache is relieved by ergotamine, the drug will continue to produce the desired results.

Recently a new drug known as dihydroergotamine (D.H.E.45)*, an ergotamine derivative, has been placed at my disposal. Each c.c. of D.H.E.45 contains 1 mg. of dihydroergotamine.

Horton, Peters and Blumenthal[2] have reported their experience with this new substance in 120 cases of migraine. In their series, seventy-nine patients showed all the features of typical migraine. Seventy-five per cent of these patients obtained good to excellent results from the use of D.H.E.45. The remaining forty-one patients had a typical migraine and only 36 per cent obtained good to excellent results with D.H.E.45. These workers found that D.H.E.45 was just as effective as

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department.

*Furnished by Sandoz Chemical Works, Inc.

ergotamine tartrate in relieving acute attacks of headache and they also observed that D.H.E.45 was three times less toxic than ergotamine tartrate.

It is interesting to note that D.H.E.45 possesses a marked sympathetic-oparalytic action similar to ergotamine but it exerts no effect on the uterus as contrasted with ergotamine tartrate.

Kirchhof and his associates[3] made observations with D.H.E.45 and epinephrine on the blood pressure of the dog and they found that D.H.E.45 is adrenolytic when subsequent injections of adrenalin are given.

Dannenberg[1] reports his observations with D.H.E.45 on several patients and found it to be as effective as ergotamine tartrate once the nature of the headache is firmly established, and he has found that best results have been obtained if it is used early in a migraine attack.

I have observed the use of D.H.E.45 in twenty-eight patients in whom the symptoms were due to various causes. Twelve of these twenty-eight patients were of unknown etiology after careful physical examination. Nine of these twelve patients obtained no marked relief from the use of D.H.E.45. Three patients were definitely relieved after the use of D.H.E.45 when given subcutaneously.

Sixteen patients had an allergic history plus associated allergic diseases such as chronic allergic rhinitis, asthma or urticaria. They also had more or less typical migraine consisting of unilateral or bilateral pulsating headache, associated with nausea and occasionally with vomiting. Previously they obtained relief only by lying down in a quiet dark room and allowing the symptoms to "wear off" inasmuch as they were not helped by any previous medication. Eleven of these allergic cases were given quicker relief by D.H.E.45 than with any previous medication and the headache generally disappeared in one to three hours. Only one patient experienced some nausea and felt "jittery" from the injection and yet this patient voluntarily returned for another injection when his headaches recurred. One other patient felt slightly nauseated. Several patients had a second injection when the first did not afford relief. In other words, if the first injection did not relieve the headache, the second usually did not.

Fourteen of the patients had from four to eight injections (one only for each attack) whenever the headaches recurred and this was over a period of four months. Two patients had had Gynergen previously and experienced side effects but after receiving injections of D.H.E.45, the headache was relieved and no side effects occurred.

In addition, all allergic patients with migraine were put on an allergic routine consisting of: (1) diet—eliminating common allergens such as cocoa, nuts, spice, shell fish, pork, juices; (2) environmental control—avoiding dust, odors, powders, feathers, animals, et cetera, wherever

practical; (3) no desensitization treatment. All previous medication had been of no value.

The allergic patients were tested intradermally, and only the most common allergens were used. These included milk, wheat, eggs, orange, potato, tomato, cocoa, coffee, house dust, pyrethrum, cottonseed, chicken feathers, mixed molds, mixed grasses and ragweed. Thirteen cases showed at least one or more definite positive reactions. All had a previous history of allergic manifestations as well as present symptoms of perennial allergic rhinitis or asthma. This group was composed of naval personnel.

The successful use of this drug in headaches of allergic origin suggests that headaches not responding to D.H.E.45 should be those most amenable to histamine desensitization. This treatment offers another clue in the differential diagnosis of headaches.

TYPICAL CASE REPORT

W. C. B., a young man, aged twenty, had chronic bronchitis and a "stuffy" nose for many years, occurring at various times of the day and worse during the night. Two years ago he developed asthma following a spell of virus pneumonia. For one and a half years, he has had headaches about once a week, usually behind the left eye but often bilateral, pulsating in character and frequently associated with nausea. His nose was congested during the headache spells. Dust and smoke caused sneezing spells. There were no known food allergies.

Physical examination was essentially normal except for a marked bilateral allergic edema of the nasal mucosa especially the turbinates. Intradermal tests using fifteen common allergens revealed 4 plus sensitivity to house dust and to chicken feathers.

Elimination diets were of no avail. Various medicines gave no relief. 1 c.c. D.H.E.45 given intramuscularly relieved him in one hour. Formerly these headaches lasted twenty-four to forty-eight hours, requiring bed rest. He was told to return at the onset of a headache for another dose of D.H.E.45. The next attack was relieved in fifteen to twenty minutes and did not recur. He was given five more injections in the next two months for similar headaches, each attack being relieved in fifteen minutes to one hour. There were no side effects or toxic reactions. The headaches have been less frequent and less severe recently. The D.H.E.45 given early in the attack, gave more prompt relief than when injected after the headache had been present for hours. This was also noticeable in other cases.

CONCLUSIONS

1. Dihydroergotamine is useful in headaches of allergic origin rather than the idiopathic type.
2. It relieves allergic migraine headaches in one to three hours.
3. The incidence of toxic or side effects is negligible.
4. Although this series of cases is small, dihydroergotamine (D.H.E. 45) promises to be a most useful agent in the symptomatic treatment of migraine and is worthy of further investigation.

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FLEABITE REACTIONS

Clinical and Experimental Observations and Effect of Histamine-Azoprotein Therapy

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THE damage caused by the flea to the human race has been depicted in its extremes in song and story. The blight of the Black Plague has been the gruesome subject of many medieval and modern medical authors, and the annoyance caused to gentle ladies of the Russian Court has been immortalized in Moussorgsky's "Song of the Flea." But in between these poles of demise and discomfort there is a middle region about which relatively little heretofore has been said or done. The author has reference to a state which has variously been referred to as allergy, hypersensitivity, sensitivity, or idiosyncrasy to fleabites. When the ordinary individual is attacked by a flea, he usually exhibits a few small, red papules, often with tiny hemorrhagic centers, and the itching is bearable and over in a few hours. In a couple of days the lesions are no longer visible.

Flea allergy may take several forms: In the localized papular form the lesions swell tremendously, getting red and hard, and itch maddeningly. The visible and subjective evidence will persist for a week or ten days. Some of these lesions will go on to give a localized bullous or purpuric form. The generalized forms may or may not be accompanied by the abnormal original local lesions mentioned. A generalized pruritis without visible lesions other than the original points of attack occurs. A widespread urticarial reaction is common and in some cases the urticaria assumes a vesicular or bullous form; these lesions may persist for two weeks. Angioneurotic edema removed from an original point of attack is rare. Asthma occurs occasionally in conjunction with the skin reaction but nasal, gastro-enteric, or migrainous symptoms are practically unknown. Needless to say, the itching may beget psychiatric problems, and the inevitable scratching often seems to make the itching worse rather than better. The other sad feature of the scratching is that, especially with children, it leads to secondary infections such as impetigo, lymphangitis, lymphadenitis, furuncles, and carbuncles, all of which can be quite serious.

Local anti-pruritic therapy is only partially successful as can be attested by the imposing list of preparations used, and when the body is completely covered becomes well nigh impossible. Prophylaxis against fleabites consists of either avoidance of exposure to fleas (such as keeping away from animals and crowded places), or treating the body, clothes, or sleeping quarters with insect repellents or insecticides. Most people do not relish the self-imposed isolation, and the repellents have the disadvantage of odor, irritation, allergenicity in themselves, and necessarily continuous

renewal. Furthermore, many insect repellents were more successful in repelling one's friends than the fleas. It was inevitable, then, that if a person wished to lead a normal life he would sustain more or less fleabites. Quite logically, therapy, acquiescing to this fact, took the direction of trying to immunize or desensitize to the ubiquitous flea. Peptones, nonspecific vaccines, and boiled milk injections were tried and were useless. Extracts prepared from the flea itself, using many extracting fluids and many extracting processes, ranging from simple maceration to the Krueger low-temperature steel ball mill pulverization, were completely ineffective in treatment. The author has tried therapy with flea extracts prepared by every means described in medical literature up to the end of 1944; it has been ineffective. Some positive skin reactions were obtained to a 1 per cent extract prepared by grinding fleas in a low-temperature steel ball mill (Krueger process) to prevent denaturization and then sterilized by Berkefeld and Seitz filtration. Even in those cases which reacted positively to this extract there was no perceptible effect with treatment.

Two factors have conspired to make assessment of the value of desensitization treatment difficult and perhaps to delude investigators into thinking they have accomplished results when they have not. The first is a natural variability in the frequency of fleabites. For some unaccountable reason there may be long periods of time in which few if any fleas are present and then they can become abnormally numerous. The second factor is a definite tendency to spontaneous auto-desensitization, which may occur just at the time that therapy is in progress. Here on the Pacific Coast it is quite frequently observed that people recently arrived from the Eastern United States are tremendously annoyed by fleas, whereas they were not in their former home. In the course of approximately a year, however, they usually experience no more difficulties from fleabites than the native Westerner. Any cases, therefore, selected for therapy should be from among newcomers during the first few months after their arrival or in residents who have had their symptoms undiminished for at least a year.

PRELIMINARY EXPERIMENTS ON NATURE OF FLEABITE REACTIONS

Epinephrine administered subcutaneously within fifteen minutes after the flea bites usually reduces the amount of local reaction and/or aborts generalized reactions. Given after this period the effect of epinephrine is only temporary. In sensitive patients presenting multiple initial lesions one may inject procaine into some of the papules, leaving the others as controls, and note that the anesthetized lesions do not become as large or persistent. In two highly sensitive volunteers who invariably developed generalized urticaria after a fleabite the author could prevent the attack by immediate electrocoagulation of the test site. After eight minutes this procedure was ineffective. An injection of histamine acid phosphate (.7 to 1.5 c.c. of 1:1000) would reproduce the clinical picture in those susceptible to systemic reactions.

The following sequence of events seems probable: The flea antigen (which is probably a digestive enzyme or anticoagulant) unites with the flea antibody of sensitized people. This union takes place on the cell membranes of skin cells with the consequent release of histamine (or similar H-substances). This reaction is usually localized in scope, but enough histamine may be absorbed into the circulation to cause reactions at remote points. The mechanical trauma of scratching releases even more H-substance from already more or less injured cells.

Other possibilities which cannot be refuted in the light of our present knowledge are that fleas inject an H-substance directly into the lesion or a toxin which kills some cells with the liberation of H-substance. The latter would be more likely than the former.

The author reasoned that whatever the mechanism of release of H-substance, its effects could be nullified by either its decomposition or neutralization. The enzyme histaminase was administered in doses of 15 units every four hours. The result was a definite but not marked diminution in the majority of cases tried, but this was abandoned because of the necessity of continuous administration. Efforts to produce neutralizing bodies by the intradermal or subcutaneous administration of histamine gave some promise but had to be abandoned because of the flushing, headache and occasional urticarial reaction or asthma produced. Histamine diffuses rapidly and is quickly detoxified. Whatever beneficial effects were noted continued only as long as treatment was kept up and were not worth the effort and discomfort involved. The author's experiences with histamine-azoprotein are now reported.

DEVELOPMENT AND ACTION OF HISTAMINE-AZOPROTEIN

Landsteiner[6] showed that the diazotization of simple chemicals and coupling to proteins resulted in the formation of an antigenic complex whose specificity was determined by the hapten portion. Recently a method has been developed for the heightening and preserving of histamine antigenicity with simultaneous elimination of its usual toxic effects and the antigenicity of the associated protein. The first step was the despeciation of horse serum globulin by partial digestion with Taka-diastase at pH 3.8 followed by neutralization.[1] The resulting globulin produced no reaction in people known to be acutely allergic to horse serum and dander. Histamine was then combined with paranitrobenzoylchloride in chloroform and triethylamine. The resulting paranitrobenzoyl histamine was then reduced with ferrous sulfate and ammonia to yield para-aminobenzoyl histamine, which was then diazotized and coupled with the despeciated globulin. The histamine-azoprotein produced was separated out, purified, and redissolved in weak alkali. This solution is adjusted to a pH of 7.4. A 3 per cent antigen solution contains .8-1.0 mg. of bound histamine per c.c.; there is no free histamine. This antigenic complex stimulates formation of his-

tamine neutralizing antibodies without producing histamine reactions.[5,7] M. Cohen showed that these bodies were specific for the histamine, not the azo or protein portion of the complex, and that in certain patients histamine-azoprotein produced a capacity for very rapid histamine neutralization.[3] He also demonstrated an increased skin threshhold to histamine administered by iontophoresis in histamine-azoprotein treated patients[3] and increased refractoriness to eserine stimulation.[4]

Sheldon and his associates treated a miscellaneous group of patients with allergic disorders and found histamine-azoprotein was of considerable value in the skin disorders.[8] M. Cohen felt that histamine-azoprotein was of particular value in the treatment of urticaria and angioneurotic edema.[2] This seemed like a promising method of treating fleabite sensitivity.

METHOD OF TREATMENT

The following succession of doses was administered subcutaneously in the region of the deltoid insertion to adults at four- or five-day intervals: 0.02 c.c., 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.65, 0.8 and 1.0 c.c. Children of six or below were stopped at the 0.65 c.c. level. Patients were advised not to change habits or surroundings and not to use insect repellents or local remedies. The only two classifications of patients were residents, fifteen in number, who had lived in San Francisco and had had symptoms over one year, and newcomers, seven in number, who had had their symptoms only two to four months. All complained of inordinate itching, local or generalized, and were subject to being bitten by fleas at intervals of two weeks or less. The sex distribution was equal.

RESULTS OF TREATMENT WITH HISTAMINE-AZOPROTEIN

The results of treatment are assembled in the accompanying table. The effects on the original bites or primary lesions and the generalized or secondary reactions (when present) are separately noted. The use of L.P.L. for large primary lesions is a space-saving abbreviation.

COMMENT

A definite response was obtained in every one of the twenty-two cases. The start of benefit was noted between the fourth and tenth injection, fifteen out of the twenty-two patients noting it between the sixth and eighth treatment. All ten patients having large primary lesions only had the size and persistence of their lesions markedly minimized. Four patients had large primary lesions and generalized pruritus but without visible secondary lesions; in these the generalized pruritus was abolished, and the primary lesions diminished in size and persistence. In the five cases in which the large primary lesions were accompanied by urticaria (and angioneurotic edema) the secondary lesions were prevented entirely, and the primary lesions minimized. The two patients whose lesions became purpuric no longer developed this feature, and the child whose large initial lesions used to have a bullous surface now had only normal reactions.

RESULTS OF TREATMENT WITH HISTAMINE-AZOPROTEIN

Age and Sex	Resident or Newcomer	Previous Duration and Type of Symptoms	Changes Accomplished by Histamine-Azoprotein Therapy	Injection at Which Improvement Noted	Post-treatment Period Under Observation
31-F	N	3 mos. LPL persisting 10 days	Smaller lesions lasting only 2 days. Less itching	5th	6 mos.
43-F	R	4½ yrs. LPL persisting 9 days.	Fewer lesions lasting only 3 days. Minim. itching.	8th	4 mos.
50-M	R	8 yrs. tremendous local and subcut. swellings at sites of bites. Generalized pruritis.	Much smaller lesions with minor local pruritis only.	10th	*5 mos.
26-F	N	2 mos. LPL and generalized urticaria	No urticaria. Size and persistence of original lesions halved.	6th	8 mos.
17-M	R	14 yrs. LPL persisting 10 days. Generalized pruritis.	Mild local pruritis only. Smaller primary lesions persisting only 4 days.	8th	4 mos.
13-F	N	3 mos. LPL and generalized urticaria for 2 days after bite.	Only ordinary local reactions. No urticaria.	4th	5 mos.
25-F	R	2 yrs. Primary lesions large and purpuric	Ordinary small papular reactions.	7th	6 mos.
6-F	R	5 yrs. LPL persisting 9 days.	Diminished reactions persisting 4 days.	6th	3 mos.
33-M	N	4 mos. LPL with urticaria & angioneurotic edema following bites	Diminished local reactions only.	8th	7 mos.
3-F	N	2 mos. LPL persisting 8 days	Lesions smaller lasting 3 days only.	5th	3 mos.
22-M	R	15 yrs. LPL persisting 10 days.	Minimal lesions for 4 days only.	8th	5 mos.
5-F	R	4 yrs. LPL persisting 8 days with urticaria	Lesions smaller, lasting 3 days. No urticaria.	6th	4 mos.
45-M	N	3 mos. LPL persisting 9 days.	Lesions smaller, lasting 5 days.	9th	5 mos.
5-M	N	4 mos. LPL persisting 7 days.	Lesions smaller, lasting only 3 days.	8th	4 mos.
28-F	R	10 yrs. LPL persisting 8 days. Gener. pruritis.	Lesions smaller, lasting 3 days. Local prur. only.	6th	†6 mos.
22-M	R	7 yrs. LPL for 9 days. Often purpuric	Lesions small, persisting 3 days. None purpuric.	7th	8 mos.
12-M	R	9 yrs. LPL persisting 7 days.	Lesions smaller, lasting 5 days.	7th	6 mos.
15-F	R	3 yrs. LPL persisting 8 days. Blotchy erythematous rash.	Lesions smaller, lasting 8 days. No erythema.	9th	5 mos.
39-F	R	6 yrs. LPL persisting 7 days.	Lesions minimal, lasting 3 days.	8th	4 mos.
10-M	R	1½ yrs. LPL persisting 10 days.	Lesions tiny. Gone in 4 days.	9th	4 mos.
4-M	R	3 yrs. LPL for 8 days with urticaria.	No urticaria. Small lesions with min. itching.	7th	3 mos.
2-M	R	2 yrs. LPL for 9 days with bullous tops	No bullae. Size and duration of lesions halved.	6th	4 mos.

*Recurrence at that time successfully re-treated.
†Recurrence at that time successfully re-treated.
LPL—Large primary lesions.

In general, the persistence of all primary lesions reduced to four days or less and the size to one-third or less; the itching was diminished not only in persistence but in intensity. Impetiginized lesions due to scratching did not occur after the eighth injection in any case. At about this point there were no complaints about disturbed sleep.

All cases were followed for a period of three to eight months, with only two recurrences, one at five months and one at six months, both successfully re-treated.

SUMMARY

1. Forms of skin reactions to fleabites are described. The exaggerated primary lesions may be accompanied by generalized skin reactions.

2. Prophylactic therapy heretofore has been unsatisfactory.

3. Experimental evidence is presented that an H-substance produced at the site of the bite is responsible for the exaggerated local and generalized reactions. The mechanical trauma of scratching increases the amount of H-substance produced.

4. Steps in the development and immunologic background of histamine-azoprotein are outlined.

5. Twenty-two patients who suffered from marked persistent local lesions or generalized skin reactions were treated by the subcutaneous injection of histamine-azoprotein.

6. Good results were obtained in every case. Generalized reactions were completely prevented and all primary lesions were diminished in size and persistence to approximately ⅓ of the former figures. Purpuric reactions in two cases and bullous reaction in one case were transformed into the normal pattern.

7. There were two recurrences after five months, both successfully retreated.

* * *

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Department of Clinical Pathology and Laboratory Procedures

DETERMINATION OF PENICILLIN-SUSCEPTIBLE STRAINS OF BACTERIA

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IN this day of rather widespread chemotherapy in the infective respiratory conditions that accompany asthma or other allergies, it occurs to me that rather careful analysis of the conditions presented by the patient must be made before we can properly evaluate the results of our treatment or can categorize those cases that are likely to respond. Particularly with the widespread popularity of inhalation penicillin therapy, I think it behooves us to attempt to learn more about these cases, that we may be able to judge in which cases the treatment is indicated and what results to expect. There are of course many factors that will have to be recorded to accumulate this type of data. At least one of the important factors to be considered is the susceptibility to penicillin of the bacterial flora of the bronchial tree or upper respiratory passages. This is relatively easy to do by a variety of techniques.

A simple technique giving good results in our own laboratory is as follows: One blood agar plate is inoculated with the sputum or nasal secretion in question. If the sputum is relatively scanty in bacteria it can be inoculated direct, but if this shows a tremendous bacterial population it would be desirable to emulsify a small particle of the sputum in 2 or 3 c.c. of sterile salt solution before plating. Care should be exercised in the plating so that a not too heavy growth is obtained. Colonies should be discreet and fairly numerous but separated from each other for best purposes. At one edge of the plate a small well is cut from the agar with a sterile instrument and two drops of penicillin solution containing 100,000 units per 5 cc. is placed in it. The plate is incubated twenty-four hours and examined. One should note the relative proportion of different types of organisms present as exhibited in the side of the plate distant from the well. The relative susceptibility of these organisms to penicillin can be evaluated from the side of the plate adjacent to the penicillin by the distance from the well that growth occurs. A highly susceptible organism should not grow closer than 2.5 cm. to the well. In this manner bacterial flora can be catalogued into several classes.

Suggestions or articles intended for this department should be submitted to Dr. L. O. Dutton, 616 Mills Building, El Paso, Texas.

1. Those that are practically 100 per cent susceptible to penicillin.
2. Those that are composed of mixed types of organisms, some being relatively susceptible, others not being susceptible at all. The non-susceptible colonies will of course grow completely up to the well.
3. Those specimens showing 100 per cent resistance to penicillin of all strains will show growth completely covering the inoculated area up to the edge of the well.

It is also suggested that desirable addition to this data would be re-studies of the sputum after penicillin therapy to determine the effects that it has had on the bacterial flora and perhaps restudies at intervals to see how long it requires for a similar flora to redevelop in the bronchial trees.

This whole procedure is a relatively simple bacteriological one and any adequately equipped bacteriological laboratory can carry this out. It is a procedure which will be quite applicable to even the small office laboratory, provided an incubator is available. Culture media may be purchased from some central laboratory or it can be made fairly simply from dehydrated culture stock, provided adequate pressure sterilization is available. An excellent substitute for the usual laboratory or hospital autoclave is the much cheaper pressure cooker that is equipped with a steam gauge.

NASAL AND SPUTUM SMEARS

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IN spite of the widespread information concerning the proper use of nasal and sputum smears in the study of the allergic patient, it is my general impression that in many instances we are failing to utilize this valuable procedure to its fullest advantage. The reason for this failure is perhaps due to two factors. The first of these is technical.

There still seems to be a rather widespread tendency to use Wright or Giemsa stain for this purpose. Due to the rather widely varying hydrogen ion concentrations of these secretions, these delicately balanced Polychrome stains do not offer uniform results. Often with them the eosinophiles are difficult to distinguish because eosinophilic granules are stained a rather dirty brown instead of the clear-cut pink or red that one expects to see. On the other hand, not uncommonly, neutrophilic cells show a rather marked pinking or reddening of the cytoplasm and on superficial examination may be misinterpreted as eosinophiles. To secure the best results with these stains one must have very thin film of

material and the cells must be separated and not embedded in too much mucus.

The use of methylene blue technique, advocated by Hansel, is far superior both in ease of application and clear-cutness of results. We have found the following technique to give us extremely uniform results and to be subject to a minimum of technical variations.

Smears are obtained either by nasal swabbing, blowing the nose into cellophane, or some slick paper, or in the case of post-nasal drippings by expectoration. Suitable portions of these specimens are spread on clean slides in the usual manner and are allowed to dry. Excessive fixation by heat is not desirable.

The slides are flooded with a thin film of eosin solution and immediately after flooding are washed in running tap water. Mild differentiation is carried out by flooding the slide briefly (a matter of ten seconds or so) with an alcohol acetone decolorizing solution. The slide is then briefly passed through the running tap water again and the final step is carried out by flooding the slide with methylene blue solution immediately washing in tap water. The whole procedure can be carried out in a matter of thirty seconds or so.

The formula for these solutions is as follows:

Eosin Solution

Eosin, yellowish, alcohol and water soluble	0.5 mg.
Ethyl Alcohol	95%

Methylene Blue Solution

Methylene Blue for Bacilli	0.3 gm.
Ethyl Alcohol 95%	30.0 c.c.
Water Distilled	100.0 c.c.
(Dissolve Dye in Alcohol—Add Water)	

Alcohol Acetone Solution

Alcohol 95% Ethyl	50.0 c.c.
Acetone CP	50.0 c.c.

With this technique we uniformly find the eosinophilic granules to be stained an intense pink, while all the other elements in the field are stained a uniform blue. The contrast is quite striking. An additional advantage of this stain is that the eosinophiles embedded in thick mucus, or in thickened portions of the smear, are stained quite as intense as those widely separated and the cells can be identified even through several layers of superimposed material.

The examination of such slides should be made first with the low power objective. The eosinophilic cells in such smears stand out readily and are detectable at this magnification. Many samples will have only scattered patches of eosinophilic cells and if the slide is not surveyed by the low power they are readily missed if the oil immersion is used for the entire examination. We cannot emphasize this too much as I have seen smears many times called negative on oil immersion examination alone, yet with the low power and a complete survey of the slides

eosinophilic areas are readily found. After the low power survey, suitable areas should be examined by the oil immersion lense to detect the type of bacteria present and also to search for eosinophilic granules which are widely disseminated through the mucus at times even though intact eosinophilic cells are not present. These granules are of equal significance to the intact cells.

The second reason for failure to obtain satisfactory information from nasal smears is the attempt to draw conclusions from inadequately obtained material or too few observations. It must be emphasized that these examinations have to be repeated before conclusive evidence can be drawn as to the character of the nasal secretions. Oftentimes the secretions are too watery and devoid of cellular elements to be of any value. And, oftentimes a superimposed infection of temporary nature will obscure the allergic nature of the exudate for a short period. Perhaps one of the most valuable uses of the nasal smears is the following of the progress of many of these cases of combined asthma and hay fever, who show periodic variations from the allergic to infective nature of the nasal reactions. Without periodic observation during these cycles of symptomology, particularly in children, one may be entirely unaware of the mixed and variable nature of the etiology of their symptoms.

I hope I may be pardoned for bringing this subject before you, as none of it of course is original with me. Doing so is prompted by my impression that too many of us are allowing this extremely valuable procedure to fail to give us the information and understanding of our cases which it is capable of giving.

D.H.E. 45 (DIHYDROERGOTAMINE) IN THE TREATMENT OF ALLERGIC MIGRAINE

(Continued from Page 130)

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Effect of Ephedrine Sulphate on the Red Blood Count of Humans. Harris, A. M., and Davis, J. E.: Proc. Soc. Exp. Biol. & Med., 54:195, 1943.

Red blood counts, leukocyte counts and hemoglobin determinations were done at frequent intervals before and after the daily administration of 50 mg. ephedrine sulphate to seven normal persons. A mild, but appreciable polycythemia was produced in three weeks; disappearing, however, in some of the subjects in the fourth week. No deleterious effects were produced.

Photograph by Fabian Bachrach

HARRY L. ROGERS, M.D.
Philadelphia, Pennsylvania
President, 1945

Editorial

The opinions expressed by the writers of editorials in the ANNALS *are individual and do not necessarily represent the group opinion of the Board or of the College.*

BLAZING THE TRAIL

Progress in allergy, as in all other specialties in medicine is dependent upon efficient organization and education. The success of organization is dependent upon the wholehearted co-operation of all its members. There must be no dissension within its ranks.

Many major advances in civilization, as well as in medicine, were made in spite of opposition and intolerance. New theories in medicine often become outmoded or disproven. Progress may be impeded, therefore, by those who adhere to their beliefs. Virchow and his associates set back our knowledge of tuberculosis twenty years because of his "dualistic theory" and resentment of Robert Koch. Our knowledge of cancer, syphilis and other diseases were also retarded for the same reason. Only by efficient organization and education can these impediments be eliminated.

Indeed, there is great need for further education and its dissemination in allergy. The problem is almost an unsurmountable one. Methods of diagnosis and treatment must be standardized. In general allergy today, there is too much individualization on the part of the allergist in the management of the patient. It is the chief aim of the College, therefore, to solve many of these problems.

The American College of Allergists was incorporated November, 1942, as a non-profit organization. The aims and purposes of the College as set forth in the charter are:

(a) The establishment of an organization of qualified medical men and scientists of good standing who shall meet from time to time for the purpose of promoting and advancing the study, research and clinical knowledge of allergy as it applies to the various specialties in medicine;

(b) To maintain and advance the highest possible standards among those engaged in the practice of allergy;

(c) To perpetuate the best traditions of medicine and medical ethics;

(d) To establish standards for the qualification and procedure for the certification of men engaged in the specialty of allergy;

(e) To maintain the dignity and efficiency of this specialty in its relation to public welfare;

(f) To promote friendly intercourse among those engaged in the practice of allergy.

Space will only permit referring to some of the things already accomplished as set forth in these clauses:

(a) The College was the first allergy society to elect as associates, immunologists, bacteriologists, pharmacologists, biochemists, plant pathologists, botanists, et cetera, and receive their valuable consultation, services, and advice.

(b) ANNALS OF ALLERGY was the first publication devoted to allergy to publish practical clinical papers as well as investigative allergy, to inaugurate an editorial, a questions and answers, a news item, and a comprehensive review of the allergy literature department. The College through the courtesy of Dr. George E. Rockwell has the use of a central laboratory for the investigation of allergens, and under his direction the first work on co-operative research in allergy by members of the College is now being successfully carried out.

Prior to establishment of the College, with the exception of an annual week-end International Forum and a two-day meeting of the Southwest Forum, there was no attempt to hold instructional courses in allergy outside of New York City. The College initiated intensive instructional courses at its first annual meeting in Chicago in 1944. Since that time a Fall course was held at St. Louis, and last November an unusually successful course was conducted for a week at Thorne Hall, Northwestern University, Chicago. The first of the annual regional instructional courses was held last month at the University of Oregon Medical School. Next November there will be an intensive course conducted by the College at the Jefferson Medical School, Philadelphia. The College was the first society to establish research fellowships in allergy. In the three and one-half years of its existence, three such fellowships have been establishd through loyal friends of the College, one at the Mayo Foundation under the direction of Dr. Charles F. Code, one at the University of Cincinnati under Dr. Matthew Logan, and recently one on Dermatologic Allergy under Drs. Stephan Epstein and Rudolf Baer.

(d) The January-February, 1946, issue of the ANNALS contained an announcement of certification in allergy by The American Society of Certified Allergists, division of the College, and reserves the right to properly qualify physicians as specialists in allergy through the American Board for the Certification of Allergists. This move was inevitable in the light of existing conditions and already applications for Certification are being received by the secretary of the new division by the most representative allergists in the United States, many now subcertified in allergy, who believe that allergy should now be recognized as a separate specialty.

The Founders Group of this new Society and the American Board for the Certification of Allergists will be composed of unquestionably qualified leaders in allergy in their respective specialties.

(f) The College is a member of the International Association of Allergists, and the first Pan-American Congress in Allergy will be held under the auspices of the College at San Francisco at its next annual session, June 28-30.

The following outline more clearly defines the functions of the three divisions of the College, which for the greater part are now operating.

We are greatly encouraged to see other allergy groups now adopting many of these plans, since there is so much to be done for allergy that earnest co-operation can never be misconstrued as duplication of effort.

THE AMERICAN COLLEGE OF ALLERGISTS, INC.

Staff of Officers

President, President-Elect, First and Second Vice Presidents, Secretary-Treasurer, Board of Regents (10 members) (Constitution and By-Laws)

Division of Education

(Separate Governing Rules and By-Laws.)

Dean, Asst. Dean, Secretary.

(1) Intensive Fall Instructional Course.

(2) Regional Spring Instructional Courses.

(3) College Annual Session—Joint meeting with The American Society of Certified Allergists.

(4) The official publication of the College — ANNALS OF ALLERGY—Spanish Supplement.

(5) Committee on Undergraduate and Graduate Education in Allergy—Speakers Bureau.

Division of Certification

The American Society of Certified Allergists.

(Separate Governing Rules and By-Laws.)

President, Secretary-Treasurer, Board of Directors.

The American Board for the Certification of Allergists.

Division of Public Relations

(Separate Governing Rules and By-Laws.)

Director, Asst. Director, Secretary.

(1) National Foundation for Allergy. (Fund raising by laymen—Annual Membership.)

A. Fund for Research.

B. Fund for Prevention of Asthma.

(2) News and Press Releases.

(3) Certification of Allergenic Extracts, Drugs, Cosmetics, etc., for Allergists.

F.W.W.

OUR GUEST SPEAKER

The College will be honored by the presence of the eminent Robert Doerr, M.D., Ph.D., Professor Emeritus of Hygiene and Bacteriology at the University of Basel, Switzerland, at the Second Annual Meeting to be held at the Clift Hotel, San Francisco, June 28, 29 and 30. On his arrival in this country he and a group of his close friends will be entertained in New York at a testimonial dinner by the College.

Doctor Doerr was born on November 1, 1871, in Téscö, Hungary. He studied in Vienna and received his M.D. there in 1897. After graduation he became a medical officer in the Austro-Hungarian army, and while in military service he specialized and qualified in general and experimental pathology, and devoted himself to scientific research in the fields of microbiology and hygiene.

During the course of an epidemic of papataci fever among the troops in Herzegovina the malady received the attention of Austrian military physicians, and in 1908 a commission consisting of Doerr, Franz and Taussig proved it to be a virus infection transmitted by the sand-fly (Phlebotomus papatassi). They were the first to prove that infected sandflies could be transported from an endemic area of the disease to a country

where it did not occur and the conditions reproduced in the latter by permitting the insects to bite human volunteers.

During the first World War Doctor Doerr was Director of the Army Bacteriological Laboratory especially concerned with sanitary conditions in the army.

In 1919, at the end of the war, he went to the University of Basel as Professor of Hygiene and Bacteriology where he has remained ever since, refusing many offers of other posts (Robert Koch Institute in Berlin, Universities of Freiburg, Monaco, Marburg).

Doctor Doerr is a member of many scientific societies and the recipient of many honors such as the Aronson prize, the Schneider gold medal from the University of Würzburg, the Marcel-Benoist prize. He is a corresponding member of several scientific societies (Swedish Academy in Lund, Académie de Médicine de Paris, et cetera).

Two Festschriften have been published in his honor; one in honor of his 60th birthday in *Zeitschrift für Hygiene und Infektionskrankheiten*, 1931, and another in honor of his 70th birthday in *Schweizerische medizinische Wochenschrift*, 1941.

His published works are too numerous to list here, although all allergists should read "Allergie und Anaphylaxie" (Handbuch d. path. Mikroorg., 1913) and "Allergische Phänomene" (Handb. d. normalen und pathologische Physiologie, 1929).

Doctor Doerr will present a paper before the College on "Integration and Differentiation of Allergic Phenomena," and is being made an Honorary Member. He will also be introduced at the Pan-American Congress, a section of the International Association of Allergists, at their session under the auspices of the College at the Clift Hotel, Friday afternoon, June 28.

COLLEGE EX-SERVICE MEMBERS—AN APPRECIATION

One of the greatest manifestations of loyalty to the College has been the unusual promptness of the members when meeting their financial obligations upon their return to civilian practice. This is the kind of stuff upon which the College has been built and which has made it possible to function as it has. The officers of the College owe a debt of gratitude to the members, about 125, who served in the late World War.

During the war there were no annual meetings or any advantages obtained by the members who remained at home. Those at home tried to keep the faith by developing the College, setting up new vital departments and placing the College on a firm financial basis when undertaking new projects, which may be beneficial to all in the College when resuming important postwar activities.

ANNALS OF ALLERGY was mailed regularly to every member in the Service. Changes of address were made with many members at least a half dozen times. It is obvious that many of these went astray, especially

when the publishers did not receive notice of a change of address. The publishers are trying to replace copies for those who have not received them. The College pays the publishers $6 for every member per year for the annual subscription to the ANNALS. This subscription is included in the annual dues.

We realize that although remittances may not have been a hardship to a number who were high-ranking officers in the Medical Corps, it was, no doubt, to others.

In the near future the College Honor Roll of those who served in the armed forces will be published in the ANNALS.

F.W.W.

SPINAL ANESTHESIA IN THE THERAPY OF PULMONARY EDEMA; A PRELIMINARY REPORT. Sarnoff, S. J., and Farr, H. W.: Anesthesiology, 5:69, (Jan.) 1944.

The authors add spinal anesthesia to the already accepted methods of reducing pulmonary edema: a sitting position by the patient and venesection. Three patients with pulmonary edema were given spinal anesthesia; 50 mg. of procaine hydrochloride per c.c. spinal fluid were administered to patients in a sitting position while leaning forward. These three cases are reported in detail. The mechanism of relief by this method cannot be stated with finality. The etiology of pulmonary edema is that the left ventricle cannot maintain stroke volume equal to that of the right, causing a pressure to be built up in the pulmonary system with extravasation of fluid into the alveoli, diminished vital capacity and hypoxia. Action of the anesthetic may be: (1) a pooling of blood in muscles, spleen, etc., with decreased return to right heart; (2) lowered peripheral resistance as result of paralysis permitting better left ventricular action; (3) diminution of subjective apprehension in these patients.

Good results are obtained without diminished hemoglobin content of the blood, as results from venesection. When the output of the ventricles is nearly equal, edema diminishes in intensity. Improvement in pulmonary edema can be accompanied by decreased cardiac output.

IMMUNITY TO TETANUS INDUCED BY A THIRD DOSE OF TOXOID THREE YEARS AFTER BASIC IMMUNIZATION; BASED ON A STUDY OF THIRTY-EIGHT ALLERGIC CHILDREN. Peshkin, M. M.: Am. J. Dis. Child., 67:22 (Jan.) 1944.

Thirty-eight allergic children were given a "booster" dose of 0.5 c.c. combined alum-precipitated diphtheria and tetanus toxoid. This was done three years after their basic immunization. A mild reaction was noted in 33 per cent of the children. One systemic reaction occurred in a child given the combined toxoids. An average of two months after the "booster" dose, scratch-test reactions with these toxoids were negative. Adequate tetanus antitoxin titers were noted within one month in all cases. This titer was higher and more prolonged than that following the basic immunization. The author recommends the use of alum-precipitated tetanus toxoid alone for this "booster" dose in order to keep local and systemic allergic reactions at a minimum level.

Progress in Allergy

HAY FEVER

A Review of the Literature for 1945

GEORGE E. ROCKWELL, M.D., F.A.C.A.
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Allergists have long been cognizant of the importance of hay fever—during 1945 it reached national importance when a bill was introduced into the Congress of the United States authorizing an appropriation of $50,000 for research with respect to the cause and cure of hay fever.*

This review on hay fever deals chiefly with the progress for the year of 1945. However, occasionally where it seemed advisable we have referred to or included earlier work. In order to clarify the work it has been organized into sections dealing with various phases of the subject. The section on drugs includes only those which are of particular interest in the treatment of hay fever; it does not represent a complete review of drugs of value in allergy.

POLLINOSIS

Distribution, Botany, and Weed Control

Harsh[30] and collaborators published an extensive survey of pollinosis in San Diego County, California, which should be particularly valuable to allergists in that district. Further, it is a model that could well be followed in making surveys of other territories. The data they present is too massive to summarize in a review so it is suggested that all who are interested in this particular subject read the original article. A pollen review of the grass season in Brazil[27] was also published. In most of the territory they report a well defined grass hay fever season extending from mid-May to mid-June. The principal offenders were Melinis Minutiflora (Capin gordura or C. Melando) and Cynodon dactylon. A symposium on allergy in the Air Surgeon's Bulletin included a paper dealing with hay fever-exciting plants in the Southwest,[5] also another on the treatment of hay fever and seasonal bronchial asthma.[56] Both of these papers are restricted and hence we have no information as to what they contain other than that indicated by their titles.

Wodehouse's "Hayfever Plants[67]" is an authoritative book dealing with pollens and pollinations and the part they play in hay fever. It contains a description of the plants known to cause hay fever, where they grow, when they flower; and a geographic regional survey with accurate and recent data on areas throughout the United States, Canada and Mexico. It is fully illustrated. Every allergist should have this text.

The rapid progress being made in the field of botany on growth regulating substances is reflected in a paper by Grigsby[28] on the large scale inhibition of pollen production in ragweed by the use of chemical sprays. They report field tests using di-nitro-secondary-butyl-phenol, penta-chlor-phenol and other chemicals but all of these are toxic to cultivated crops. Greenhouse experiments showed that 2-4 D and other similar materials in low concentration stopped the growth of the terminal buds

*Oct. 3, 1945, Mr. Lane of Mass. introduced H. R. Bill 4279.

of ragweed. The leaves remained green but no pollen was produced over a two-month period. They suggest that such a spray might prevent the production of pollen by common ragweed without having the undesirable feature of complete destruction of vegetation. They plan to try this in extensive field experiments.

To the writer's knowledge no new papers have been published on the much discussed subject of X hay fever. However, Dr. Homer Prince writes to us as follows: "We do see certain cases of hayfever that do not appear to be readily diagnosed. We feel that these cases occur the year round. When they occur in the winter, we attribute them to house dust, respiratory infections, and what-have-you. But when they occur in the summer we do not so readily think of the infections, and since we feel that house dust cases should not have trouble in the summer we presume that additional causes must exist. Apparently in Houston we do not have quite as many of these patients as there are further east. Furthermore, there will be years when we will have more of them. I think it is fairly well concluded that there are no undiscovered pollens causing these symptoms. Molds seem to be about the only thing left that would likely be responsible for the trouble. The various molds that have been cultured will not diagnose all cases, although here and there cases are relieved with various mold extracts. Molds that fall into the basidiomycetes might be particularly responsible. These comprise the rusts and smuts and related forms, and apparently they must be secured from their hosts for extraction which further complicates the problem."

ATMOSPHERIC STUDIES

Courtright and Courtright[15] presented a well-controlled and extended study on the reactions of 350 guinea pigs which were sensitized and shocked by inhalants of horse dander under various weather conditions. Their results definitely indicated that the weather condition affects the reaction of the animal. This article is well worth reading.

Brown, et al.[9], in a statistical study, found that there were an increased number of new colds during periods of falling temperature accompanied by heavy rains; also that smokers showed an increased tendency towards colds.

This is a fascinating subject and any allergist who has treated a group of hay fever or asthma patients is well aware of the effect of the weather on the welfare of his patients. Atmospheric studies together with filtration methods certainly should be worthy of extensive study.

POLLEN THERAPY

Dosage, Delayed Absorption, Insoluble Antigens, Booster Dose, Immune Studies, Oral Therapy, and Adjuvants

Acceptance of the treatment of hay fever by inoculation with pollen extract brought new troubles to the physician, for in trying to get the patient to sufficiently high dosage for protection he encountered both local and systemic reactions. The systemic reactions were particularly undesirable and in order to eliminate them the dose was increased less rapidly which necessitated many more injections. Various lines of investigation were pursued in an attempt to obviate these difficulties, and from these experiments several schools of thought developed.

One on low dosage therapy was championed by Hansel. During the past year he published a paper[29] on this therapy in which he described the method of intradermal testing to determine the size of the initial dose together with subsequent intradermal treatment with these minute doses. For these purposes he uses extracts varying from 1:100,000,000 to 1:1,000 concentration. He states that in testing he never uses more than the 1:1,000 dilution except in the very rare case in which he may use the 1:100 dilution. The writer has had no experience with low dosage therapy except in very hyper-sensitive patients in which cases we have been amazed and gratified by the

excellent clinical results although the maximum dose was very low, but never as low as the doses advocated by Hansel. Some allergists complain of poor results when using the low dosage therapy. Perhaps this is due to their method of use. It is the writer's conviction that the greatest value of this therapy is in selected cases as we feel that the maximum tolerated dose for hay fever cases is the one which gives the best results. However, it is possible that there are two mechanisms of protection, namely: one evoked by the low dosage therapy, and the other evoked by high dosage therapy.

Another group advocated reducing the rate of absorption by suspending the antigen in oil. No recent papers have been published on pollen oil mixtures. However, Gay[28] reported on the nonantigenic properties of beeswax and showed that a mixture of beeswax and oil was adaptable for slowing the absorption of injected penicillin. This might be worthy of consideration in the case of pollen extract.

Others made and used the alum precipitate of the pollen antigen. The alum-precipitated pollen antigen seemed to increase sensitivity instead of decreasing it. Nothing has developed on this method recently and we believe its use has been abandoned.

It had previously been found that the hydrochloride of the pollen antigen was relatively insoluble and therefore slowly absorbed. These qualities make it particularly adaptable for immunization in hay fever cases because its use permits a more rapid increase of dosage with a higher top dose; reduces the visits of the patients; gives much better clinical results; and minimizes systemic reactions. Its clinical use is gradually increasing. Its biggest disadvantage is that it is a little more difficult to prepare. However, in the reprints of the lectures of the 1945 American College of Allergists Instructional Course[51] specific directions are given for making and using this pollen antigen hydrochloride. If the allergist is either too busy or does not have the necessary laboratory equipment for its preparation, it is available commercially.*

A number of decades ago Besredka introduced the sensitized vaccine by treating the bacteria with their immune serum. Later toxin and antitoxin mixtures were developed and now we find Cohen and Friedman[14] reporting on the preparation of a mixture of pollen antigen and its thermostable antibody serum together with its use on three cases. This report is not very impressive because: (1) conclusions have been made on only three treated cases. (2) The maximum dose given one of these cases was only 5,000 units for ragweed and another was 7,500. In the Ohio area this will give little or no protection to a severe ragweed case. Since these patients had no symptoms the inevitable conclusion must be that they were mild cases of hay fever. (3) It is claimed that by the use of this antigen antibody mixture they are able to effect this protection with fewer doses. Based on the size of these doses they can be practically duplicated with pollen antigen hydrochloride.

Following the advent of the booster dose which was particularly emphasized in the production of immunity to tetanus with tetanus toxoid, Loveless introduced its application to the treatment of hay fever.

The principle of the booster dose is based upon the assumption that protection to hay fever is due to the development of an immunity. In order to substantiate this method of treatment it became necessary to prove that this protection is due to the establishment of immunity. In continuing her studies on immunity, Loveless[47] recently described the technique of the conjunctival test as a guide to clinical immunity in hay fever. She concluded that it reveals the threshold of reaction and thus is an important clinical guide to the amount of specific treatment required by the hay fever patient. Those having a threshold of 350 or better are more apt to have excellent clinical results than those having 35 or less. These figures in themselves cause one to ponder. For one thing her experiments showed that 49 per cent of those having a titre of 35 or less showed satisfactory clinical results. Further, in what class are

*Delapan. Eli Lilly and Company.

those between 35 and 350? Finally, this data was collected on the eastern seaboard. What about the central states of Ohio, Indiana, and Illinois where the pollen exposure is much higher? When one sees the appearance of an eye with a good reaction he has the distinct feeling that he would not wish to have it happen to his own eye.

By means of precipitation tests Johnson et al.[38] have demonstrated the presence of ragweed antigen in the sera of hay fever patients. They proposed to study the correlation among the amount of this circulating antigen, thermo-stabile antibody, and reagins; also the relation of these values to the dosage of pollen extract and the pollen count.

Alperstein[2] described an agglutination test wherein pollen-antigen-coated bacteria were used. Cavelti[13] described improvements in the technique of collodion agglutination. However, it is the writer's opinion that neither the collodion nor the bacterial coated agglutination tests are practical at their present development.

About a decade after Noon introduced pollen therapy in 1911, papers began to appear on the desensitization to hay fever by ingestion of the pollen antigen. This interest in oral therapy is manifested because of the many apparent advantages that it offers namely: no injections, minimum reaction, does not require as frequent visits to the doctors office, and most important makes possible the desensitization of certain persons who would otherwise receive no treatment.

Landau and Gay[43] reported moderate to poor results on the use of propeptans in the treatment of ragweed hay fever. In earlier work Iliff and Gay[34] reported that of 82 ragweed patients treated with oral therapy three obtained excellent relief, 10 had good results, and 39 had fair benefit.

Thiberge[62] published an article in which he concluded that oral pollen therapy in the form of enteric coated pills is effective and may be advantageously used as a supplement to parenteral pollen therapy or in patients who cannot avail themselves of parenteral treatment. He again concluded, as he has in the past, that gastric digestion destroys the activity of the ragweed-pollen antigen. However, he has failed to take into consideration experiments previously reported.[52] In this work it was shown that any loss which occurs in acid pepsin digestion of the ragweed antigen is not due to the digestion, but rather to two factors: oxidation of the antigen; and removal by filtration of the insoluble pollen antigen hydrochloride which is formed. This loss can be prevented by excluding oxygen during the process of digestion, or by the addition of dextrose; and by the neutralization of the digestive mixture before filtration.

It has been the writer's experience that oral therapy in the grass type of hay fever is as effective as parenteral therapy.

Urbach[64,65] reported further extensive studies in animals on oral sensitization and oral de-allergization. These studies were carefully executed and the results are impressive. He presented controlled animal experiments which show that sensitization can be brought about orally and that with certain methods de-allergization can be accomplished by the oral administration of propeptans. The conditions of these experiments are so given that they should be capable of repetition, and it would be well for those who disagree with this theory to repeat these experiments.

Adjuvants have been used in the production of immunity and we now find Kulka and Hirsch[40] reporting that rabbits and guinea pigs were more highly sensitized to ragweed extracts when it was given in conjunction with killed tubercle bacilli, paraffin oil, and Aquaphor. Further the antibody level was more sustained. Boyd[7] found that the addition of a good antigen such as killed Monilia to a poor antigen such as hemoglobin enhances the antibody response to the latter. The results reported in the above two papers might explain why some observers get better results when using a cold vaccine along with ragweed immunization than they do with ragweed immunization alone.

Walzer[66] found that ragweed as well as several other antigens could be transported by electrophoresis through three subjects in the same circuit. Any number of sensitized sites reacted to transported antigen when they were covered with negative saline poles.

COLLATERAL SENSITIZATION

In the past there have been numerous papers on the importance of collateral sensitization in the successful therapy for hay fever. We feel that during recent years this subject has been neglected both in research studies and in its application by the allergists. We mention it here not because there are any new developments to report but with the hope that it will recall to the allergist the importance of this subject.

HAY FEVER PANEL DISCUSSION

During the past year the International Correspondence Club of Allergy under the direction of Dr. Forman conducted an open discussion on hay fever. A questionnaire was solicited among the members and the replies appeared in the Club Letters. The first question asked was, whether the observer was satisfied to obtain a marked degree of relief for the patient or whether he insisted on having the patient free of symptoms. Very few of the responses indicated any hope of a *permanent cure* for hay fever; certainly examples are rare. Most observers replied that they strived for complete relief of symptoms for the patient, but more than half of them were satisfied with marked relief.

Another question concerned the results actually obtained. Many of the allergists in the ragweed area reported 90 to 100 per cent results after the first season of treatment. Generally these high figures referred to cases of uncomplicated hay fever. More than half considered 75 per cent results to be satisfactory. Constitutional reactions have been minimized by careful observation of the patient's reaction, adjustment of dosage, and cautious technique.

The survey showed the perennial type of treatment was preferred by most observers. However, the type of treatment frequently depended upon the time of the season at which the patient presented himself, and hence pre-seasonal and co-seasonal treatments were used extensively. It was learned that in most instances treatment was not entirely discontinued during the hay fever season: many continued on a greatly reduced dose at longer intervals. No general estimate of the maximum dose used can be made since the replies covered such a wide range.

Another question asked how much emphasis was placed on other factors such as diet, swimming, nursing aids, etc. The replies indicated that almost 90 per cent do place some emphasis on these other factors, particularly on diet. It was learned that an overwhelming percentage do not use respiratory vaccines as part of their routine treatment. When used at all the vaccines were generally stock preparations.

Some critics suspect the allergists of adopting a ritual to impress the patient. This was greatly discredited by those replying to the questionnaire. Most of them claimed to have a standard procedure which was designed to impress the patient with the importance of following instructions minutely, but they all insisted that psychology cannot do much to convince the patient that he does not have hay fever.

DRUGS

Hapamine, Vitamin C, Ethylene Disulphonate, Antihistamine, Butanefrine, and Nasal Sprays

Hapamine (Histamine-azoprotein) was introduced to the profession for the development of immunity or desensitization to histamine. In the past several years numerous papers have reported good to indifferent results with Hapamine: during

1945 the International Correspondence Club of Allergy published several letters on this subject.

Edrington[19] and Braden[8] each reported a case of severe systemic shock following a small injection of Hapamine. In each case the patient was cleared of allergic symptoms following the very severe shock. Freund[23] described a reaction to Hapamine in which the patient developed a fever of 103° and showed glandular enlargement. Epstein[20] reported two cases which developed neuritis while receiving Hapamine. He suggested that before administering Hapamine, intradermal tests be done with 0.02 c.c. of a 1/10 dilution of Hapamine, and also scratch tests with Parke Davis purified horse protein. If both of these tests are negative, he feels that it should be safe to use Hapamine. On the other hand Hawkins[33] wrote that she had no less than phenomenal results with very small doses of Hapamine in cases of neuritis and even arthritis. Bowen[6] treated six cases of ragweed pollinosis with Hapamine and reported six failures.

Friedlaender and Feinberg[24] studied Vitamin C in the treatment of a series of hay fever cases. They concluded that hay fever patients had a normal blood level of Vitamin C, and that doses of 500 mgs. daily did not change the course of hay fever or asthma. Brown et al.[9] suggested that Vitamin C possibly acts on the virus of the common cold.

Ethylene disulphonate is still the subject of much controversy. Recent work includes a report by Kurland and Bubert[42]; one by Archibald[3]; a paper presented by Ketcham[39] at the meeting of the Southern Medical Association; and a great deal of discussion in the letters of the International Correspondence Club of Allergy[35], which also gave a complete bibliography of ethylene disulphonate. It is our impression that allergists are of the general opinion that ethylene disulphonate is of little or no value.

New compounds have been prepared which are claimed to have anti-histamine action. Loew et al.[45,46] described the action of beta dimethylaminoethyl benzhydryl ether hydrochloride (benadryl). Mayer and co-workers[48] have developed several anti-histamine compounds similar in their action; one of them, No. 63, shows promise of therapeutic value. Proceedings of the staff meetings of the Mayo Clinic[50] included a symposium of benadryl and its use in urticaria, bronchial asthma, hay fever, physical allergies, et cetera. It was reported that of fifty-two hay fever cases, 75 per cent were benefited. There were certain side effects of the drug including drowsiness, nervousness, trembling, and inco-ordination. In hay fever 50 mgs. twice daily gave many patients almost complete relief, and in most instances this dose was sufficiently small to avoid side effects. Feinberg and Friedlaender[21] reported favorably on its use in urticaria, serum sickness, rhinitis, and possibly asthma. We have used this drug in several cases of urticaria. It gave relief during continued administration but when discontinued the condition returned. It has also given relief in one out of three cases of asthma in which it was used and it has proved of great benefit in several cases of vasomotor rhinitis. Besides the side effects above noted, two of our patients taking 50 mgs. six times a day developed an acute gastrointestinal upset. This drug may prove to be a very valuable adjunct in the management of hay fever.

Lehmann and Young[44] reported good results on the antihistamine activity of diethylaminoethyldihydroanthracine-carboxylate in animal experiments.

Butanefrine is a drug with an epinephrine-like action but differing in a few important characteristics. It requires about twice the dosage employed with epinephrine. It apparently gives equivalent relief in asthma, and although the allergist may use it more in asthma he may still find it a beneficial drug in the relief of hay fever patients. It lacks the pressor effect of epinephrine hence the vasoconstrictor action makes it available for cardiac asthma and less effective in infected cases. Tremor

and nervousness occur less frequently. We have found this drug particularly valuable in treating children, and for patients who have become senstive to adrenalin itself. Papers first appeared on butanefrine in 1917 and have continued regularly throughout the years. For those who are particularly interested in this compound we are including a complete bibliography.[10,11,12,16,26,31,32,37,49,55,57,58,59,60,61]

Much has been written on the use of various nasal sprays. Feinberg and Friedlaender[22], Kully[41], and Thomas[63] all issued warnings on the prolonged use of nasal vasoconstrictors, particularly Privine.

Abramson and Demerec[1] described a method for controlling particle size in the use of therapeutic aerosals: many constructive ideas are given. Rothman et al.[54] found group specificity present in a man sensitive to procaine.

CHEMISTRY

Berresford and Cooke[4] reported their studies on pollen moisture and the hygroscopic nature of pollens. Commercial air-dried pollens were found to have a moisture content from 4.6 to 19.6 per cent. They advise that pollens should be machine dried; sealed in air-tight containers and sent at once to the laboratory. Upon receipt at the laboratory they recommend that the pollens be defatted immediately and stored under vacuum.

Rockwell[53] read a paper before the American Chemical Society which presented further proof of the structure of the active antigens in ragweed pollen. A method was given for separating the various antigens as the hydrochlorides: namely by addition of 7.5 c.c. of concentrated HCl to each 100 c.c. of a 10 per cent extract. One antigen is precipitated within a few hours as the hydrochyoride. This antigen contains only one molecule of carbohydrate; the remaining antigens are much smaller in molecular size and each molecule contains several molecules of carbohydrate, hence they are much more soluble and do not immediately precipitate out as the hydrochloride. However, if allowed to stand in the cold in the presence of the hydrochloric acid, the carbohydrate is converted to furfural and methylfurfural until each antigen contains only one molecule of carbohydrate, at which point it precipitates out as the hydrochloride. In this way each fraction can be separated and purified. Analytical data was given to show that all of these antigens are carbohydrate-flavonol-peptide complexes somewhat similar to Warburg's yellow oxidation enzyme. Molecular weights vary from the largest which is 4496.084 to the smallest which is approximately 640. All of these fractions are immunologically and biologically active.

STANDARDIZATION

Standardization of allergens has been the target for several editorials. In the letters of the International Correspondence Club of Allergy[36] it was stated that standardization was not of particular interest but "clinical dependability and results are important." This reflects absolute confusion, for the purpose of standardization is to strive for consistent clinical dependability and results.

One editorial[18] brought up the question of whether or not there is more than one antigen in an extract; possibly one which functions as a skin reactive factor; and one which is effective in treatment.

The American Academy of Allergy voted that "as a temporary expedient, pollen quantity as described in published papers and presented talks shall be explained in terms of units in which one unit is equivalent to quadruple 0 one (0.00001) mgs. of nitrogen as precipitated by phosphotungstic acid."

A controversial editorial[17] pointed out the futility of such a standardization and suggested that possibly the successful standardization of allergens will have to be both biological and chemical. The chemical standardization should be placed upon a

scientific basis such as molar standardization. Molar standardization has the advantage of being the only method proposed which would furnish information on the relative amounts of various antigens present in one extract.

The Standardization Committee of the American College of Allergists is executing an extensive experimental program on standardization; studying both biological and chemical aspects. The report of their data and conclusions when made available should advance our knowledge on this subject. In previous reports they showed that in both pollen and dust extracts there was a marked similarity between biological activity and molar units; whereas other experimental evidence presented showed that this was not true when based upon total nitrogen and phosphotungstic acid precipitate nitrogen.

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(Continued on Page 157)

Questions and Answers

In contact dermatitis of the lips, clinically proved to be caused by lipstick, what is the ingredient most commonly causing this condition?
M.D., Portland, Oregon.

The causes of lipstick sensitivity, in order of frequency, seem to be perfume, indelible dye (tetrabromofluorescein), coloring materials, and the base itself.

There are two methods of determining the specific cause of the dermatitis, namely, patch testing by the usual method and also clinical testing on the lips. It is advisable to patch test the patient first and to test clinically only in those cases where the patient does not react to patch tests or in order to verify negative patch test results.

Unscented lipsticks and lipsticks without indelible dye are readily available. Some manufacturers of hypo-allergenic cosmetics carry special stock products and offer lipstick in additional bases and in several special colors. They also make individual formulas where required.

PROGRESS IN ALLERGY

(Continued from Page 156)

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✶ *In Memoriam* ✶

MAXIMILIAN ARTHUR RAMIREZ, M.D., F.A.C.A.

The College is deeply shocked at the recent death of one of its Active Fellows, Dr. Maximilian Arthur Ramirez, of New York City, on March 4, 1946, at the age of fifty-four.

Dr. Ramirez received his medical education at the University and Bellevue Hospital Medical College, New York, where he graduated in 1912. He was born in Cuba on May 17, 1891; he was professor of medicine at the New York Polyclinic Medical School and Hospital; specialist certified by the American Board of Internal Medicine; past president of the Medical Society of the County of New York; fellow of the American College of Physicians and the New York Academy of Medicine.

Dr. Ramirez served during World War I, and was attending Chief and Director of the Second Medical Division of the French Hospital, and was made Chevalier of the French Legion of Honor.

He was attending physician, New York City Hospital, Welfare Island, as well as Municipal Sanatorium, Otisville; consulting physician, St. Francis Hospital, Poughkeepsie, St. Agnes Hospital, White Plains, and Downtown Hospital.

The College extends its sincere sympathy to the members of his family. We shall feel his loss keenly.

ALLERGY AND TUBERCULOUS TRACHEOBRONCHITIS. Oatway, W. H., Jr., Gale, J. W., and Mowry, W. A., J. Thoracic Surg., 13:1, (Feb.) 1944.

The authors have observed that many patients with tracheobronchial lesions had clinical evidence of an allergic diathesis. One hundred patients were bronchoscoped in an attempt to decide the presence or absence of a tuberculous tracheal or bronchial lesion and its characteristics. A complete examination was done and then allergic studies were carried out. Testing was done by the scratch and the intradermal methods. Tuberculin tests were done with a dilution of O.T. of 0.01 mg. and 1.0 mg. Of the 100 patients, eighty had some evidence of tuberculous tracheobronchitis. Of these, 75 per cent were women. Of the eighty patients, fifty were studied completely from the allergic view. There was a correlation between a personal history of allergy and the presence of tuberculous bronchitis by bronchoscopic examination. All the patients reacted to O.T. but there was no association between such reactions and the allergic history. Patients with tuberculous bronchitis were more allergic to routine allergens (by skin test) than were the patients without tuberculous bronchitis. Attempts to desensitize patients with tuberculous tracheobronchitis using tuberculin, do not seem indicated. Desensitization of these patients to other allergens is indicated and legitimate.

News Items

Through Dr. Irving Schiller of Boston $50 was contributed towards the Research Fund by Mr. George Sibley of the College-Town Sportswear, Boston.

* * *

Jack A. Rudolph, Major, MC, Oliver General Hospital, Augusta, Georgia, has recently been appointed Chief of the Medical Service.

* * *

Dr. Frederick Reiss, 816 Fifth Avenue, New York, has been appointed Attending Dermatologist to the Allergy Clinic of the Manhattan Eye, Ear and Throat Hospital and also Consultant to the Surgeon General of the U. S. Army.

* * *

Dr. Isabel J. Wolfstein, who was formerly located at 760 Bankers Trust Building, Indianapolis, Indiana, is now located at 2412 Euclid Heights Blvd., Cleveland Heights 6, Ohio.

* * *

Dr. Samuel S. Burden, Captain, MC, has been transferred from the A.S.F. Regional Hospital at Camp Crowder, Missouri to the Walter Reed General Hospital, where he is now Chief of the Allergy Clinic.

* * *

As the ANNALS goes to press, we sorrowfully regret to announce the death of Dr. William Duke of Kansas City on April 10. A biographical sketch of Doctor Duke will appear in the next issue.

* * *

Dr. Marion Sulzberger is now Associate Director of the Skin and Cancer Unit of the New York Postgraduate Hospital, Columbia University. Dr. Rudolf Baer is in charge of the Allergy Department under the service of Dr. Fred Wise at this same Unit.

* * *

Dr. Henry I. Shahon, 104 Elm Hill Avenue, Roxbury 21, Massachusetts, formerly Major, M.C., at the Veterans Administration, West Roxbury, Massachusetts, is now out of the service, but has been appointed Consultant Allergist to the Veterans Administration.

* * *

At the Spring Instructional Course held at the Universtiy of Oregon Medical School, Portland, March 4 through 6, inclusive, five scholarships for the Course at a reduced rate were granted to residents and interns of the Medical School, who were recommended by Dean David Baird. These scholarships were made possible by the Almay, Inc., Grant for undergraduate education in allergy.

* * *

The Southeastern Allergy Association met in Atlanta, Georgia, March 30 and 31 at the Atlanta-Biltmore Hotel. Dr. Hal McCluney Davison of Atlanta, Georgia, was elected president. Dr. J. Warrick Thomas of Richmond, Virginia, was elected Vice President, and Dr. Katharine Baylis MacInnis of Columbia, South Carolina, was elected Secretary-Treasurer. Dr. Marion Davidson of Birmingham, Alabama, and Dr. David Thomas of Augusta, Georgia, were elected to the Executive Council from the membership at large. There were fifty-two doctors registered for the meeting.

NEWS ITEMS

We are pleased to announce the return from service of the following members of the College and their present locations: Lt. Comdr. Lewis Brown, 162 Roseville Ave., Newark, N. J.; Captain Lewis J. Dimsdale (MC), 18 Blackstone, Sioux City, Iowa; Captain William S. Eisenstadt (MC), 1743 Medical Arts Building, Minneapolis, Minnesota; Captain Meryl M. Fenton (MC), David Broderick Tower, Detroit, Michigan; Major I. M. Hinnant (MC), 10465 Carnegie Avenue, Cleveland, Ohio; Lt. Colonel Louis E. Lieder (MC), 327 Osborn Building, Cleveland 15, Ohio; Captain Lawrence L. Rackow (MC), S. E. Co. 77th Avenue and Limekiln Pike, Philadelphia 38, Pennsylvania; Lt. Colonel James W. H. Rouse (MC), Nix Professional Building, San Antonio, Texas; Captain Harry Paul Schenck, 1912 Spruce Street, Philadelphia, Pennsylvania; Lt. Harold O. Schneider (MC), Salem Clinic, Salem, Oregon; Captain Berthold M. Stern (MC), 6400 North Park Avenue, Philadelphia 26, Pennsylvania; Lt. Colonel Boen Swinny (MC), Medical Arts Building, San Antonio 5, Texas.

SECOND INTER-AMERICAN CONGRESS OF CARDIOLOGY

The Second Inter-American Congress of Cardiology will be held in Mexico City, from the 6th to the 12th of October, 1946. All Cardiological Societies of the Continent will take part in the Congress, and, as guests of honor, eminent European cardiologists have been invited to attend.

Doctor Mario Salazar Mallén is secretary of the organization, and he cordially invites any members of the College who might be interested to attend and take part in this Congress. Those wishing to obtain further information about the Congress or the trip to Mexico should write directly to the offices of the Congress, Calzada De La Piedad No. 300, Mexico, D.F., Mexico.

BOUND VOLUMES AVAILABLE

The College has contracted with the Dahl Binding Company, Minneapolis, Minnesota, to bind Volumes 2 and 3 of the ANNALS OF ALLERGY. Volume 2 includes the six issues for the year 1944. Volume 3 is comprised of the six issues for 1945.

For those wishing to obtain complete sets, the price for the two volumes will be $15.00, including binding, postage and handling. The binding is of special dark green buckram on pressboard. Subscribers who have copies of all their ANNALS in good condition for binding can have them bound for $1.50 per volume if sent to the Office of the Secretary-Treasurer, so that they may be included in this lot; otherwise, binding of single volumes will be $3.00 per volume.

THE REVOLUTION IN RESPIRATORY PHYSIOLOGY

Anoxia has been proven to be a depressant, not a stimulant, to the C.N.S. The same is true of its effect on the respiratory center and even the respiration is stimulated by reflexes in carotid and aortic bodies. Hence breathing is likely to cease when severe anoxemia is removed. Gas tensions and acidity of arterial blood are now thought to be results rather than causes of pulmonary ventilation. The balance between nervous and chemical factors in respiration is disturbed by narcotic drugs. The single effect of all narcotics is to decrease sensitivity of respiratory center to increased CO_2 tension in the blood. Narcotics also tend to shift the balance of respiration to the carotid and aortic body reflexes control. Then the dominant factor in respiratory control is reflex aroused by anoxemia. The respiratory center may cease functioning when these reflexes are abolished by CO_2 administration. The author advises other means of stimulating the respiratory center.—C. F. SCHMIDT, Anesthesiology 5:77 (Jan.) 1944.

BOOK REVIEWS

SKIN DISEASES IN CHILDREN. By George M. Mackee, M.D., and Anthony C. Cipollaro, M.D. Second Edition Revised and Enlarged. 448 pages. 225 illustrations. Price $7.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers.

This book is a clear, concise up-to-the-minute presentation of the diagnosis and therapy in the very important field of pediatric dermatology by two widely experienced clinicians and teachers.

There are twenty-one chapters covering the diagnosis and modern therapeutic material of all of the cutaneous affections of infancy and childhood. The fungus disease and diseases due to animal parasites are given in detail.

Of particular interest to allergists is the excellent chapters on Allergic Dermatoses in Children (by Frances Pascher, M.D.); the Eczema Group, The Erythema Group and Dermatitis Medicamentosa or Drug Eruption. The latter half of the text presents Benign and Malignant New Growths, Congenital Cutaneous Anomalies (by Eugene F. Traub, M.D.); The Scaling Dermatoses and the Lichens; Pigmentary Affections; Diseases of the Sweat and Sebaceous Glands, Hair and Nails; the Vesicular and Bullous Diseases; the Contagious Diseases and the Tuberculosis and Syphilis Group of Skin Diseases. The last chapter on Syphilis is written by Herman Beerman, M.D.

Under treatment practical and used prescriptions are given throughout the book along with specific therapeutic measures. The book is very well bound, the print is large and the illustrations are superb when bringing out the details so necessary when illustrating skin diseases.

The use of this book should not be limited to pediatricians, and all physicians particularly the allergists should avail themselves of this important new text.

—F.W.W.

THE 1945 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. By Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. 559 pages. 72 illustrations. Price $3.00. Chicago: The Year Book Publishers, 1945.

Although published annually, it is astonishing the amount of new material which appears each year indicating the great advances of our knowledge of Dermatology and Syphilology. With the availability of penicillin its increased combined use with the old antisyphilitic agents is giving promising results.

Detailed observations of studies made on the use of DDT in cutaneous infestations, on the role of fatty-acid powders in the prevention and treatment of certain fungous infections and on chick embryo culture of the micro-organism causing granuloma inguinale are presented.

The continuation of fundamental studies concerning the skin and carcinogenesis, vascular reactions and the psyche and emotions are also reported. The authors stress the importance of the skin in human physiology and morbidity and its value as an organ for scientific research.

The first half of the book is devoted to the leading article dealing with drug eruptions including a detailed discussion of the Atabrin eruption observed during World War II; treatment and preventive measures of common dermatologic diseases; physical therapy; eczema, urticaria and allergy; drug eruptions; hematogenous

dermatoses; other dermatoses; tumors; fungous and other infections; infestations; and venereal diseases.

The remainder of the book presents nearly a hundred pages on investigative studies in skin and venereal diseases. There is a very complete index, the paper of improved quality and the illustrations are good.

The authors have succeeded in awakening new interests in this r[illegible] panding field which deserves greater support in the universities, hospita[illegible] field of research. To be up to date with our knowledge of dermatology a[illegible]hilology, every physician should have this new 1945 edition.

-F.W.W.

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